Chapter 30: Hypertension

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 10, Hypertension.

KEY CONCEPTS

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1. The risk of cardiovascular (CV) morbidity and mortality is directly correlated with blood pressure (BP).

2. Evidence definitively demonstrates that antihypertensive drug therapy substantially reduces the risks of CV events and death in patients with high BP.

3. Essential hypertension is usually an asymptomatic disease. A diagnosis cannot be made based on one elevated BP measurement. An elevated BP value from the average of two or more BP measurements, present during two or more clinical encounters, is required to establish a diagnosis of hypertension.

4. The overall goal of treating hypertension is to reduce associated morbidity and mortality from CV events. Antihypertensive drug therapy should be selected based on evidence demonstrating CV event reduction.

5. A goal BP of <130/80 mm Hg is appropriate for nearly all patients with hypertension.

6. The magnitude of BP elevation should be used to guide the number of antihypertensive agents to start when implementing drug therapy. Most patients with stage 1 hypertension should start on one medication as initial therapy. Most patients presenting with stage 2 hypertension should be started on two medications as initial therapy.

7. Lifestyle modifications should be prescribed to all patients, especially those with elevated BP and hypertension.

8. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazides are preferred first-line antihypertensive agents for most patients with hypertension. These first-line options are for patients with hypertension who do not have a compelling indication for a specific antihypertensive drug class.

9. For most patients with hypertension, β-blocker is not an appropriate first-line treatment. While β-blocker will reduce CV events in hypertension compared to no treatment, it will not reduce CV events as much as has been demonstrated with an ACEi, ARB, CCB, or thiazide.

10. Compelling indications are comorbid conditions where specific antihypertensive drug classes have been shown in clinical trials to reduce CV events in patients with these specific comorbidities.

11. Older patients are often at higher risk for adverse reactions related to antihypertensive medications. Antihypertensive drug therapy selection should be the same as in younger patients, but lower initial doses should be used to minimize the risk of side effects in older patients.

12. Patients are categorized as having resistant hypertension when they fail to achieve goal BP while adherent to a regimen that includes three antihypertensive agents (one of which includes a diuretic) at full doses, or when four or more antihypertensive agents are needed to treat hypertension regardless of goal BP achievement.

13. Alternative antihypertensive agents should only be used in combination with first-line antihypertensive agents to provide additional BP lowering because they do not have sufficient evidence demonstrating CV event reduction.

BEYOND THE BOOK

BEYOND THE BOOK

Clinical Interaction: Patient with Hypertension

Prepare for this activity by completing the following tasks:

- View the instructional video "How to Use Your Home Blood Pressure Monitor" at: https://www.youtube.com/watch?v=K9HU2F3TOaI.
- Read the iForumRx.org commentary and listen to the podcast episode "Ten Things Every Clinician Should Know About the 2017 Hypertension Guidelines" available at: https://iforumrx.org/commentary/ten-things-every-clinician-should-know-about-the-2017-hypertension-guidelines/.

Complete the activity by doing the following:

- Identify a patient with hypertension that has been prescribed two or more antihypertensive agents.
- Measure a patient's BP using the technique demonstrated in the video.
- Engage in a brief discussion with your patient and address the following topics related to hypertension:
  - How long has the patient had hypertension?
  - What strategies does the patient use to take their antihypertensive medications regularly?
  - What does the patient believe are the benefits of the current antihypertensive drug regimen?
  - What does the patient identify as some of the risks of their current antihypertensive drug regimen?
  - How well does the patient think the drug therapy regimen is working?
  - What is the patient's goal BP?
  - Has the patient taken any other antihypertensive medications in the past and how did he/she respond to them?
  - What lifestyle modifications does the patient engage in to help control BP?
- At the end of this interview, write some brief notes about this patient encounter.

INTRODUCTION

Hypertension is a common disease that is defined as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be "essential" for adequate perfusion of vital organs during the early and middle 1900s, it is one of the most significant risk factors for cardiovascular (CV) disease for decades. Therefore, increasing awareness and diagnosis of hypertension and improving BP control with appropriate treatment are considered critical public health initiatives to reduce CV morbidity and mortality.

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults is the evidence-based clinical guideline in the United States to manage hypertension.[1] The 2017 ACC/AHA guideline provides recommendations on the definition of high BP, the diagnosis, patient evaluation, treatment goals, and management in various patient populations and provides additional strategies to improve BP control. This chapter incorporates relevant components of the 2017 ACC/AHA high BP guideline and additional evidence from clinical trials and meta-analyses, focusing on the pharmacotherapy for hypertension.

Pooled data from 2011 to 2014 indicate that approximately 103.3 million Americans aged 20 years and above met the definition of hypertension according to the 2017 ACC/AHA guideline.[2] More than half (53.4%) of the US adults taking antihypertensive medications had a BP above treatment goal. Considering the health consequences associated with high BP, there remain many opportunities for clinicians to improve the care of patients with

hypertension.

EPIDEMIOLOGY

The definition of hypertension changed with the 2017 ACC/AHA guideline from a BP of ≥140/90 to ≥130/80 mm Hg. Hence, the prevalence of hypertension has increased considerably. According to the ACC/AHA definition, almost half (46%) of American adults aged 20 years and older have hypertension.[2] Although the overall prevalence has increased, only 1.9% would require additional drug therapy as the majority of newly diagnosed patients would require nonpharmacologic treatment only.[2]

The overall incidence of hypertension is similar between men and women but varies depending on age. The prevalence of high BP is higher in men than women before the age of 65 and is similar between the ages 65 and 74. However, after the age of 74, more women have high BP than men.[1] Prevalence rates are highest in non-Hispanic Blacks (59% in men, 56% in women), followed by non-Hispanic Whites (47% in men, 41% in women), non-Hispanic Asians (45% in men, 36% in women), and Hispanics (45% in men, 42% in women).[1]

BP values increase with age, and hypertension (persistently elevated BP values) is prevalent in older patients. The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is higher than 90%.[1] Most patients have elevated BP before being diagnosed with hypertension, with most diagnoses occurring between the third and fifth decades of life.

ETIOLOGY

Hypertension usually results from unknown pathophysiologic etiology (*essential* or *primary hypertension*). While this form of hypertension cannot be cured, it can be controlled. A smaller percentage of patients have a specific cause of their hypertension (*secondary hypertension*). There are many potential secondary causes of hypertension. If identified, hypertension in these patients can be mitigated or potentially be cured.

Primary Hypertension

Over 90% of individuals with high BP have essential or primary hypertension.[1] Numerous potential mechanisms have been identified that contribute to the pathogenesis of essential hypertension, so identifying the exact underlying abnormality is not possible. Genetic factors may play a role in developing essential hypertension by affecting sodium balance or other BP regulating pathways.

Secondary Hypertension

Secondary hypertension, where either a comorbid disease or a drug (or other product) is responsible for elevating BP (see Table 30-1), is much less common than primary hypertension (up to 10%).[1] In most cases, renal dysfunction resulting from severe chronic kidney disease (CKD) or renovascular disease is the most common secondary cause. Certain drugs (or other products) can directly or indirectly increase BP. The most common agents are listed in Table 30-1. 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.[1]

TABLE 30-1

Secondary Causes of Hypertension*a*

Diseases

- Chronic kidney disease
- Cushing's syndrome
- Coarctation of the aorta
- Obstructive sleep apnea
- Parathyroid disease
- Pheochromocytoma
- Primary aldosteronism
- Renovascular disease
- Thyroid disease

Medications

- Amphetamines (eg, amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, phendimetrazine, phentermine)
- Antivascular endothelin growth factor agents (bevacizumab, sorafenib, sunitinib)
- Corticosteroids (cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone)
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Decongestants (pseudoephedrine, ocular phenylephrine)
- Ergot alkaloids (ergonovine, dihydroergotamine, methysergide)
- Erythropoiesis-stimulating agents (erythropoietin, darbepoetin)
- Estrogen-containing oral contraceptives
- Nonsteroidal anti-inflammatory drugs—cyclooxygenase-2 selective (celecoxib) and nonselective (aspirin [at higher doses], choline magnesium trisalicylate, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tolmetin)
- Testosterone
- Others: desvenlafaxine, venlafaxine, bupropion

Special situations with medications

- β-Blocker or centrally acting α-agonists (when abruptly discontinued)
- β-Blocker without α-blocker first when treating pheochromocytoma
- Use of a monoamine oxidase inhibitor (isocarboxazid, phenelzine, tranylcypromine) with tyramine-containing foods or certain drugs

Street drugs and other products

- Cocaine and cocaine withdrawal
- Methamphetamine
- Ephedra alkaloids (eg, Ma huang), "herbal ecstasy," other analogs
- Anabolic steroids
- Ergot-containing herbal products
- St. John's wort

Excessive consumption of food substances

- Sodium
- Ethanol
- Licorice

[a]Agents of most clinical importance.

PATHOPHYSIOLOGY

Multiple physiologic factors control BP, and abnormalities of these factors are potential contributing components in developing essential hypertension. These include malfunctions in either humoral (ie, the renin–angiotensin–aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal 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. No one factor is probably solely responsible for essential hypertension.

Arterial BP

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

$$\mathrm{MAP} = \left(\mathrm{SBP} \times \frac{1}{3}\right) + \left(\mathrm{DBP} \times \frac{2}{3}\right)$$ MAP=(SBP×13)+(DBP×23)

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 (CO) and total peripheral resistance (TPR) according to the following equation:

$$\mathrm{BP} = \mathrm{CO} \times \mathrm{TPR}$$ BP=CO×TPR

CO is the primary determinant of SBP, whereas TPR largely determines DBP. In turn, CO is a function of stroke volume, heart rate, and venous capacitance. Table 30-2 lists physiologic causes of increased CO and TPR and correlates them to potential mechanisms of pathogenesis.

TABLE 30-2

Potential Mechanisms of Pathogenesis

Blood pressure (BP) is the mathematical product of cardiac output and peripheral resistance. Elevated BP can result from increased cardiac output and/or increased total peripheral resistance.	
Increased cardiac output	Increased cardiac preload: • Increased fluid volume from excess sodium intake or renal sodium retention *Venous constriction:* • Excess stimulation of the renin–angiotensin–aldosterone system (RAAS) • Sympathetic nervous system overactivity
Increased peripheral resistance	Functional vascular constriction: • Excess stimulation of the RAAS • Sympathetic nervous system overactivity • Genetic alterations of cell membranes • Endothelial-derived factors Structural vascular hypertrophy: • Excess stimulation of the RAAS • Sympathetic nervous system overactivity • Genetic alterations of cell membranes • Endothelial-derived factors • Hyperinsulinemia

Under normal physiologic conditions, arterial BP fluctuates throughout the day following a circadian rhythm. BP decreases to its lowest values during sleep, followed by a sharp rise starting a few hours before awakening, with the highest values occurring midmorning. BP also increases acutely during physical activity or emotional stress.

Classification

The classification of BP in adults (aged 18 years and older) is based on the average of two or more properly measured BP values from two or more clinical encounters (Table 30-3).[1] According to the ACC/AHA, there are four BP categories: normal, elevated, stage 1 hypertension, and stage 2 hypertension. Elevated BP is not a disease category but is associated with increased adverse CV risks compared to patients with normal BP.[3] It identifies patients whose BP is likely to progress to hypertension in the future, and thus for whom lifestyle modifications should be enacted to attenuate this progression.

TABLE 30-3

Classification of Blood Pressure in Adults (Age ≥18 Years)[a]

Classification	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)
Normal	<120	and	<80
Elevated	120-129	and	<80
Stage 1 hypertension	130-139	or	80-89
Stage 2 hypertension	≥140	or	≥90

[a]Classification is determined based on the average of two or more properly measured seated BP values from two or more clinical encounters. Out-of-office measurements should be used to confirm the diagnosis. If systolic and diastolic BP values yield different classifications, the highest category is used for the purpose of determining a classification.

Hypertensive crises are clinical situations where patients have extreme BP elevations, typically >180/120 mm Hg. They are categorized as either *hypertensive emergency* or *hypertensive urgency*. Hypertensive emergencies are extreme BP elevations that are accompanied by acute or progressing end-organ damage. Hypertensive urgencies are extreme BP elevations without acute or progressing end-organ injury.

Cardiovascular Risk and Blood Pressure

1 Epidemiologic data demonstrate a strong correlation between BP and CV morbidity and mortality.[4] Risk of hypertension-associated complications (eg, stroke, myocardial infarction [MI], angina, heart failure [HF], kidney failure, early death from CV causes) is directly correlated with BP. Starting at a BP of 115/75 mm Hg, the risk of CV disease doubles with every 20/10 mm Hg increase.[1] Therefore, patients with elevated BP have an increased risk of CV disease.

2 Treating patients with hypertension with antihypertensive drug therapy reduces the risk of CV events. Evidence from large-scale placebo-controlled clinical trials has repeatedly shown that the increased risks of CV events and death associated with elevated BP are reduced substantially by antihypertensive drug therapy (see Treatment section).[5-8]

SBP is a stronger predictor of CV disease than DBP in adults aged 50 years and older; it is the most important BP parameter for most patients.[1] Patients are considered to have *isolated systolic hypertension* when their SBP values are elevated (ie, ≥130 mm Hg) and DBP values are normal (ie, <80 mm Hg). Isolated systolic hypertension is believed to result from pathophysiologic changes in the arterial vasculature, consistent with aging, that result in decreased compliance of the arterial wall and portend an increased risk of CV morbidity and mortality. A higher than normal pulse pressure (SBP minus DBP) is believed to reflect the extent of atherosclerotic disease in older patients and is a measure of increased arterial stiffness. Higher pulse pressure values are directly correlated with the risk of CV mortality.

Humoral Mechanisms

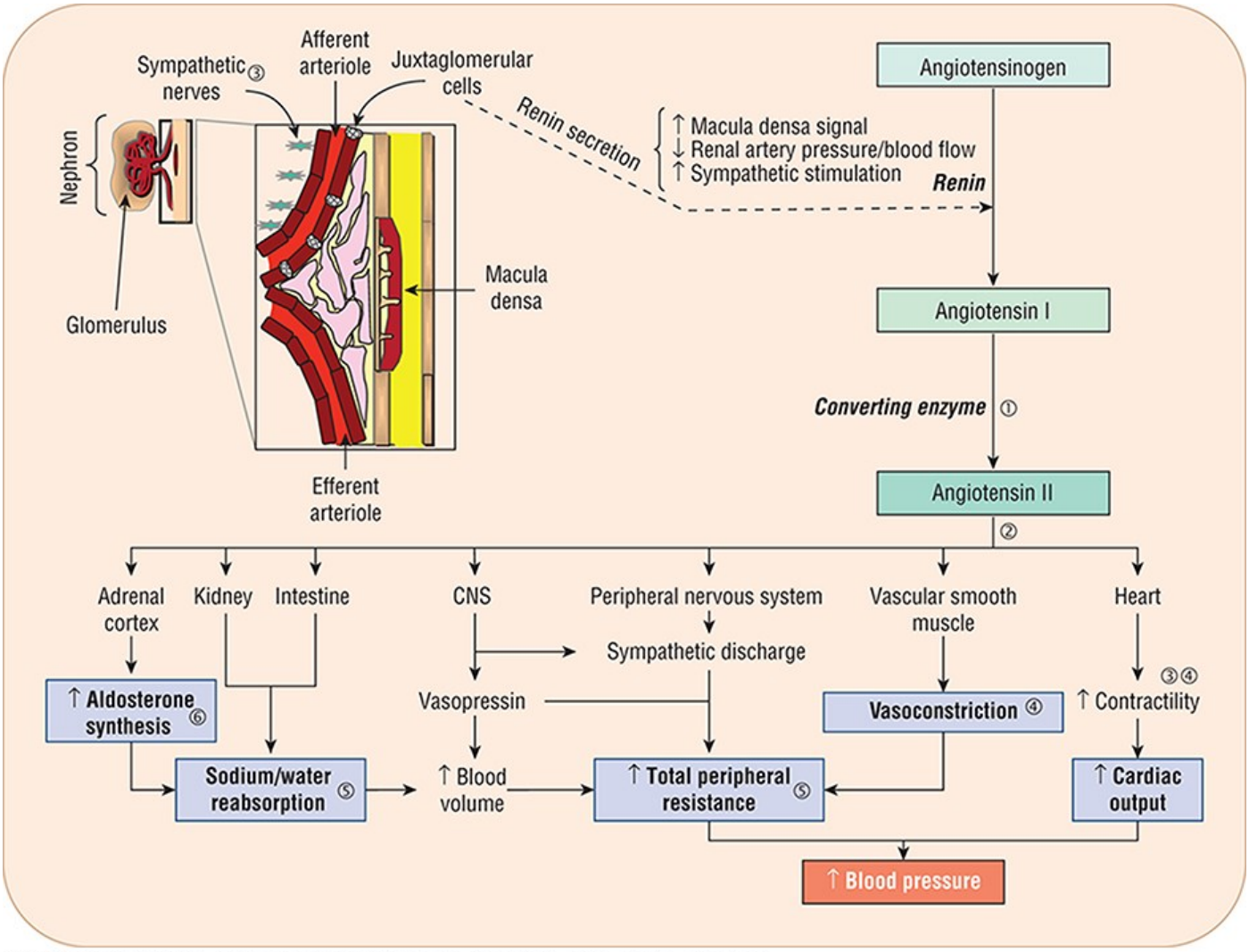
Several humoral abnormalities involving the RAAS, natriuretic hormone, and hyperinsulinemia may be involved in developing essential hypertension.

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 (see Fig. 30-1). The RAAS regulates sodium, potassium, and blood volume. Therefore, this system significantly influences the vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP.

FIGURE 30-1

Diagram representing the renin–angiotensin–aldosterone system. The interrelationship between the kidney, angiotensin II, and regulation of blood pressure is depicted. Renin secretion from the juxtaglomerular cells in the afferent arterioles is regulated by three major factors that trigger the conversion of angiotensinogen to angiotensin 1. The primary sites of action for major antihypertensive agents are included: ① ACE inhibitor; ② angiotensin II receptor blocker; ③ β-blocker; ④ calcium channel blocker; ⑤ thiazide; ⑥ mineralocorticoid receptor antagonist.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

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

Juxtaglomerular cells function as a baroreceptor-sensing device. Decreased renal artery pressure and kidney blood flow are sensed by these cells and stimulate renin secretion. A decrease in sodium and chloride delivered to the distal tubule stimulates renin release. Catecholamines increase renin release, most likely by directly stimulating sympathetic nerves on the afferent arterioles that, in turn, activate the juxtaglomerular cells.

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 angiotensin II type 1 [AT_1] or angiotensin II type 2 [AT_2] subtypes), angiotensin II exerts biologic effects in several tissues. AT_1 receptors are located in the brain, kidneys, myocardium, peripheral vasculature, and adrenal glands. These receptors mediate most responses that are critical to CV and kidney function. AT_2 receptors are located in the adrenal medullary tissue, uterus, and brain. Stimulation of the AT_2 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, leading to sodium and water reabsorption, increasing plasma volume, TPR, and ultimately BP. Aldosterone also has a deleterious role in the pathophysiology of other CV diseases (eg, HF, MI, kidney disease) by promoting tissue remodeling leading to myocardial fibrosis and vascular dysfunction. Clearly, any disturbance that leads to activation of the RAAS could explain chronic hypertension.

Natriuretic Hormone

Natriuretic hormone inhibits sodium and potassium-ATPase and thus interferes with sodium transport across cell membranes. Inherited defects in the kidney's ability to eliminate sodium can cause increased blood volume. A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water.

Neuronal Regulation

Central and autonomic nervous systems are intricately involved in the regulation of arterial BP. Many 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. Stimulation of presynaptic α-receptors (α_2) exerts a negative inhibition on norepinephrine release. Conversely, 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 tissues innervated by the sympathetic nervous system. However, in some tissues, β_1-receptors predominate (eg, heart), and in other tissues, β_2-receptors predominate (eg, bronchioles). Stimulation of β_1-receptors in the heart increases heart rate (chronotropy) and force of contraction (inotropy), whereas stimulation of β_2-receptors causes vasodilation in arteries and veins.

The baroreceptor reflex system is the primary 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 BP rapidly activate baroreceptors that then transmit impulses to the brain stem through the ninth cranial nerve and vagus nerve. In this reflex system, a decrease in arterial BP stimulates baroreceptors, causing reflex vasoconstriction, increased heart rate, and increased force of cardiac contraction. However, baroreceptor reflex mechanisms may be less responsive in older patients and those with diabetes.

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

Neuronal mechanisms regulate BP and maintain homeostasis. Pathologic disturbances in any of the four major components (autonomic nerve fibers, adrenergic receptors, baroreceptors, and central nervous system) could chronically elevate BP. These systems are physiologically interrelated. A defect in one component may alter normal function in another. Therefore, cumulative abnormalities may explain the development of essential hypertension.

Peripheral Autoregulatory Components

Abnormalities in renal or tissue autoregulatory systems could cause hypertension. For example, renal defects in sodium excretion may develop, which can then cause resetting of tissue autoregulatory processes resulting in a higher BP. The kidney usually maintains a normal BP through a volume-pressure adaptive mechanism. When BP drops, the kidneys respond by increasing retention of sodium and water, which leads to plasma volume expansion that increases BP. Conversely, when BP rises above normal, renal sodium and water excretion increase to reduce plasma volume and CO.

Local autoregulatory processes maintain adequate tissue oxygenation. When tissue oxygen demand is normal to low, the local arteriolar bed remains relatively vasoconstricted. However, increased metabolic demand triggers arteriolar vasodilation that lowers peripheral vascular resistance (PVR) and

increases blood flow and oxygen delivery.

Defects in 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 PVR and, if sustained, would also thicken the arteriolar walls. This pathophysiologic component is plausible because increased TPR is a common underlying finding in essential hypertension.

Vascular Endothelial Mechanisms

Vascular endothelium and smooth muscle play essential roles in regulating blood vessel tone and BP. Regulating functions are mediated by vasoactive substances that are synthesized by endothelial cells. It has been postulated that a deficiency in local synthesis of vasodilating substances (eg, prostacyclin and bradykinin) or excess vasoconstricting substances (eg, angiotensin II and endothelin I) contributes to essential hypertension.

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

Electrolytes

Population-based studies demonstrate that high-sodium diets are associated with a high prevalence of stroke and hypertension. Conversely, low-sodium diets are associated with a lower prevalence of hypertension. Clinical studies have shown 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 not known.

Alterations in calcium and potassium may also 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 and alterations in vascular smooth muscle function. Dietary potassium intake is inversely related to BP and may blunt the effect of sodium on BP.[1] Potassium depletion may also increase PVR, but the clinical significance of small serum potassium concentration changes in relation to BP is unclear. While altered calcium and potassium may play a role in the development of hypertension, data demonstrating reduced CV risk with supplementation are limited.

CLINICAL PRESENTATION

Diagnostic Considerations

Hypertension is called the *silent killer* because most patients do not have symptoms. The primary physical finding is persistently increased BP. The diagnosis of hypertension cannot be made based on one elevated BP measurement. The average of two or more BP measurements taken during two or more clinical encounters is required to diagnose hypertension.[1] This BP average should be used to establish a diagnosis and then classify the initial stage of hypertension using Table 30-3. Out-of-office measurements should be used to confirm elevated readings.

Measuring BP

The measurement of BP is a medical screening tool and should be conducted at every healthcare encounter.[1]

Cuff Measurement

The most common method to measure BP in clinical practice is the indirect measurement of BP using an oscillometric device or sphygmomanometry. The AHA describes the appropriate procedure to measure BP indirectly.[9] The measurement equipment (ie, inflation cuff, stethoscope, and manometer) must meet national standards to ensure maximum quality and precision with measurement.

The AHA stepwise technique is recommended:

1. Patients should ideally refrain from nicotine and caffeine ingestion for 30 minutes, have emptied his/her bladder, and sit with lower back supported in a chair. Their bare arm should be supported and rest near heart level. The feet should be flat on the floor (with legs not crossed). The measurement environment should be relatively quiet and ideally provide privacy. Measuring BP in a position other than seated (supine or standing

position) may be required under special circumstances (eg, suspected orthostatic hypotension, dehydration).

2. Measurement should begin only after a 5-minute period of rest in the seated position.
3. Neither the patient nor the clinician measuring the BP should talk during measurement.
4. A properly sized cuff (pediatric, small, regular, large, or extra-large) should be used. The inflatable rubber bladder should cover at least 80% of arm circumference and a width that is at least 40% of arm circumference.
5. The palpatory method should be used to estimate the SBP:
   a. Place the cuff on the upper arm with the bottom resting 2 to 3 cm above the antecubital fossa and attach it to the manometer.
   b. Close the inflation valve and inflate the cuff to 70 mm Hg. Palpate the radial pulse with the index and middle fingers of the opposite hand.
   c. Inflate further in increments of 10 mm Hg until the radial pulse can no longer be palpated.
   d. Note the pressure at which the radial pulse is no longer palpated. This is the estimated SBP.
   e. Rapidly release the pressure in the cuff by opening the valve.
6. The stethoscope (either diaphragm or bell) should be placed on the bare 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 and then the cuff inflated to 30 mm Hg above the estimated SBP from the palpatory method. The valve should then be slightly opened to slowly release pressure at a rate of approximately 2 mm Hg/s.
7. The clinician should listen for Korotkoff sounds with the stethoscope. The first phase of Korotkoff sounds is the initial presence of clear tapping sounds indicating cardiac contraction. Note the pressure at the first recognition of these sounds. This is the SBP. As pressure deflates, note the pressure when all sounds disappear, right at the last sound. This is the DBP.
8. Record the SBP and DBP to the nearest even number (eg, 145 mm Hg rounded up to 146 mm Hg).
9. A second measurement should be obtained after 1 to 2 minutes. If the two measurements (SBP and/or DBP) differ by more than 5 mm Hg, additional measurement(s) should be obtained.
10. When first establishing care with a patient, BP should be measured in both arms. If consistent inter-arm differences exist, the arm with the higher value should be used.

Inaccuracies with indirect measurements result from inherent biologic variability of BP, errors related to incorrect technique, and the white coat effect.[9] Variations in BP occur with environmental temperature, the time of day, meals, physical activity, posture, alcohol, nicotine, and emotions. In the clinical setting, standard BP measurement procedures (eg, appropriate rest period, correct technique, wrong cuff size) are often not followed, which results in incorrect estimation of true BP. In addition, variations may occur between individuals measuring BP. Due to these factors, the use of oscillometric devices is generally preferred.

Approximately 15% to 20% of patients have *white coat hypertension*, where BP values rise in a clinical setting but are normal in nonclinical environments as measured with home or ambulatory BP (ABP) monitors.[1] Interestingly, the rise in BP dissipates gradually after leaving the clinical setting. This is in contrast to *masked hypertension*, where a decrease in BP occurs in the clinical setting.[1] With masked hypertension, home BP is much higher than the in-office BP measurement. This situation may lead to undertreatment or lack of treatment for hypertension. While white coat hypertension is associated with a minimal increase in CV events, masked hypertension increases the risk similar to those with sustained hypertension. Moreover, patients with either white coat or masked hypertension are at higher risk of progressing to sustained hypertension.[10]

Pseudohypertension is a falsely elevated BP measurement. It may be seen in older patients, those with long-standing diabetes, or those with CKD due to rigid, calcified brachial arteries.[9] In these patients, the true arterial BP, when measured directly with intraarterial measurement (the most accurate BP measurement), is much lower than that measured using the indirect cuff method.

ABP monitoring using an automated device records BP at frequent time intervals (eg, every 15-30 minutes) throughout a 24-hour period.[9] Home BP monitoring is performed by patients or a caregiver, preferably in the morning. Upper arm devices are preferred over wrist monitors because of concerns regarding the precision of readings. Many wrist monitors are not validated, and positioning of the device (directly over the radial artery) is essential, and the wrist must be placed directly over the heart. However, a validated wrist monitor may be an option for patients whose arm measurements with home devices are difficult or not possible (eg, manual dexterity, extreme obesity). Patients should be counseled to obtain BP monitors that have been validated (see https://www.validatebp.org).

Home BP monitoring values and ABP values are often lower than clinic-measured values, particularly as BP increases beyond elevated to stage 1 and stage 2 hypertension.[1] For example, a clinic BP of 130/80 mm Hg corresponds to a home BP reading of 130/80 mm Hg and a 24-hr ABP of 125/75 mm Hg. However, a clinic BP of 140/90 mm Hg corresponds to a home BP monitoring value of 135/85 mm Hg and a 24-hours ABP value of 130/80 mm Hg.

Neither ABP nor home BP monitoring is needed for the diagnosis of hypertension, but they are recommended. These modalities are needed to identify patients with white coat or masked hypertension.[1] In addition, ABP monitoring may be a stronger predictor of all-cause and CV mortality than clinic measurements.[11] The 2017 ACC/AHA guideline recommends out-of-office measurements for diagnostic confirmation and to assist in titrating antihypertensive medication.[1] ABP monitoring may be helpful for patients with apparent drug resistance, hypotensive symptoms while on antihypertensive therapy, episodic hypertension (eg, white coat hypertension), and autonomic dysfunction, and in identifying “nondippers” whose BP does not decrease by >10% during sleep and who may portend an increased risk of hypertension-associated complications.

Limitations of ABP and home BP measurements include the complexity of use and costs. Although home BP monitoring is less complicated and less costly than ambulatory monitoring, patients may omit or fabricate readings or have a poor technique (eg, not resting for an adequate period, improper placement, wrong cuff size). Therefore, patients should be educated on the appropriate selection of a home BP device (eg, validated machine, ideally has a memory feature, right cuff size) and how to use it correctly.

Clinical Evaluation

The most common sign of essential hypertension is increased BP. The rest of the physical examination may be completely normal. However, a complete medical evaluation 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 complications. All patients with hypertension should have the tests described in the Clinical Presentation box before initiating antihypertensive drug therapy.[1] For patients *without* a history of atherosclerotic cardiovascular disease (ASCVD), CKD or diabetes, it is also important to estimate future risk of ASCVD using the Pooled Cohort Equations calculator. This calculator estimates the 10-year risk of clinical ASCVD (defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke) and lifetime risk in certain patients (found at http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/).

CLINICAL PRESENTATION: Hypertension

General: May appear healthy or may have additional CV risk factors:

- Age (≥55 years for men, ≥65 years for women)
- Diabetes (type 1 or type 2)
- Dyslipidemia
- Albuminuria
- Family history of premature CV disease
- Overweight (body mass index [BMI] 25-29.9 kg/m^2) or obesity (BMI ≥ 30 kg/m^2)
- Physical inactivity
- Tobacco use

Symptoms: Usually none related to elevated BP.

Signs: Previous BP (SBP or DBP) values in the elevated or the hypertension category.

Routine laboratory tests: Blood urea nitrogen (BUN)/serum creatinine with estimated glomerular filtration rate (using CKD-EPI Creatinine Equation [2021]; available at *https://https://www.kidney.org/professionals/kdoqi/gfr_calculator*), lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium, calcium), hemoglobin and hematocrit, and electrocardiogram. 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 tests: Echocardiogram, spot urine albumin-to-creatinine ratio, uric acid

Hypertension-related complications: The patient may have a previous medical history or diagnostic findings that indicate the presence of hypertension-associated complications:

- Brain (stroke, transient ischemic attack, dementia)
- Eyes (retinopathy)
- Heart (left ventricular hypertrophy [LVH], angina, prior MI, prior coronary revascularization, HF)
- Kidney (chronic kidney disease [CKD])
- Peripheral vasculature (peripheral arterial disease [PAD])

Secondary Causes

The most common secondary causes of hypertension are listed in Table 30-1. A complete medical evaluation should provide clues for identifying secondary hypertension. Patients with secondary hypertension might have signs or symptoms suggestive of the underlying disorder. 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 hyperaldosteronism, 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 (eg, moon face, buffalo hump, hirsutism). Patients with coarctation of the aorta may have higher BP in the arms than in the legs and diminished or even absent femoral pulses. Patients with renal artery stenosis may have an abdominal systolic-diastolic bruit.

Laboratory tests may also help identify secondary hypertension. Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, red 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 hyperaldosteronism, and plasma renin activity, captopril stimulation test, renal vein renin, and renal artery angiography for renovascular disease.

Certain drugs and other products can increase BP (see Table 30-1). 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 suggests drug-induced BP elevation.

Natural Course of Disease

The onset of hypertension is usually preceded by increased BP values that are in the elevated BP category. BP values may fluctuate between elevated and normal levels for a period of time. As the disease progresses, PVR increases, and BP elevation becomes chronic.

Hypertension-Associated Complications

Several complications can result from high BP in patients with hypertension (see Clinical Presentation box). CV events (eg, MI, cerebrovascular events, kidney failure) 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.

Hypertension accelerates the development of atherosclerosis and stimulates left ventricular and vascular dysfunction. These pathologic changes are thought to be secondary to both a chronic pressure overload and a variety of nonhemodynamic stimuli. Atherosclerosis in hypertension is accompanied by the proliferation of smooth muscle cells, lipid infiltration into the vascular endothelium, and enhancement of vascular calcium accumulation.

Cerebrovascular disease is a consequence of hypertension. Either gross neurologic deficits or a slight hemiparesis with some incoordination and hyperreflexia is 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 (TIAs) secondary to atherosclerosis in the carotid arteries can also develop in patients with hypertension.

Retinopathies can occur in hypertension and may manifest as a variety of different findings. A funduscopic examination can detect hypertensive retinopathy, which manifests as arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes (nicking), retinal hemorrhages and exudates, and disk edema. Focal arteriolar narrowing, retinal infarcts, and flame-shaped hemorrhages usually suggest an accelerated or malignant phase of hypertension (seen in some hypertensive emergencies). Papilledema (swelling of the optic disk) is usually only present in hypertensive emergencies.

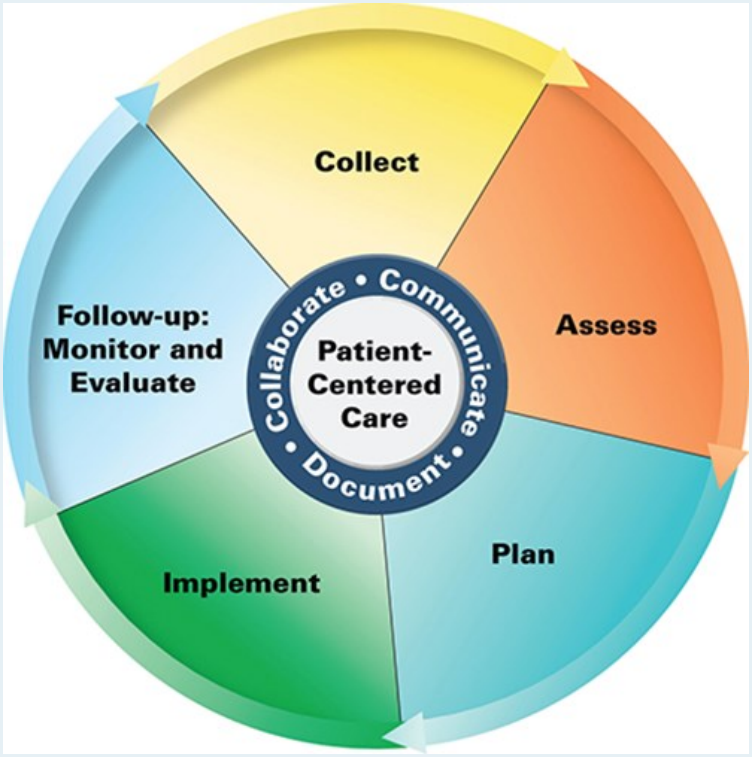
Heart disease is a commonly identified complication of hypertension. A thorough cardiac and pulmonary examination can identify cardiopulmonary abnormalities. Clinical manifestations include stable ischemic heart disease (angina, prior MI, prior coronary revascularization), acute coronary syndromes (aka, acute MI), and HF. These complications may lead to cardiac arrhythmias, angina, MI, and sudden death. Stable ischemic heart disease (also called *coronary artery disease* or *coronary heart disease*) and associated acute coronary syndromes (also called *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, followed by persistent albuminuria and then a gradual decline in kidney 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. Overt kidney failure is an important cause of end-stage kidney disease, especially in Black patients, Hispanic persons, and Native Americans.

The peripheral vasculature is a target organ affected by hypertension. 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 (PAD) is a clinical condition that can result from atherosclerosis.

PATIENT CARE PROCESS

Patient Care Process* for the Management of Hypertension



Collect

- Patient characteristics (eg, age, race, sex, pregnant)
- Patient history (past medical, family, social—dietary habits, tobacco use)
- Home blood pressure (BP) readings
- Current medications and prior antihypertensive medication use
- Objective data (see Box 30-1.)
  - BP, heart rate (HR), height, weight, and body mass index (BMI)
  - Labs (eg, serum electrolytes, Scr, BUN)
  - Other diagnostic tests when indicated (eg, electrocardiogram [ECG])

Assess

- Presence of compelling indications (eg, stable ischemic heart disease, chronic kidney disease; see Fig. 30-3)
- Hypertension-related complications (eg, albuminuria, retinopathy; see Box 30-1.)
- 10-year atherosclerotic cardiovascular disease (ASCVD) risk when indicated
- Current medications that may contribute to or worsen hypertension

- BP goal and whether the goal has been achieved (see Box 30-2.)
- Appropriateness and effectiveness of the current antihypertensive regimen
- For resistant hypertension if taking three or more antihypertensive medications (see Table 30-8)

Plan*

- Tailored lifestyle modifications (eg, diet, exercise, weight management; see Table 30-4)
- Drug therapy regimen including specific antihypertensive(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 30-5, 30-6, 30-7, and 30-9)
- Monitoring parameters including efficacy (eg, BP, CV events, kidney health), safety (medication-specific adverse effects), and timeframe (see Table 30-10)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Self-monitoring of BP, HR, and weight—where and how to record results
- Referrals to other providers when appropriate (eg, physician, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine BP goal attainment
- Presence of adverse effects
- Occurrence of CV events and development/progression of kidney impairment
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Overall Goal of Treatment

4 The overall goal of treating hypertension is to reduce morbidity and mortality from CV events (eg, acute coronary syndromes, cerebrovascular events, HF) and kidney disease. Therefore, the specific selection of antihypertensive drug therapy should be based on evidence demonstrating a reduction in morbidity and mortality, not merely a reduction in BP.

Blood Pressure Goals

5 Treating patients with hypertension to achieve a desired goal BP is a surrogate goal of therapy. Reducing BP to a goal does not guarantee the prevention of hypertension-associated complications but significantly lowers risk. Targeting a goal BP is the standard of care for how clinicians

evaluate response to therapy. It is the primary method used to determine the need for titration and regimen modification.

The 2017 ACC/AHA guideline recommends a goal BP of <130/80 mm Hg for the management of hypertension in most patients (Box A), including those with ASCVD, diabetes, or chronic kidney disease.[1] The American Diabetes Association recommends a minimum goal of <140/90 mm Hg for patients with diabetes and lowers CV risk, with a lower goal of <130/80 mm Hg for certain individuals (eg, those at higher risk of ASCVD) if achieved without undue treatment burden.[12] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend an SBP goal of <120 mm Hg for patients with CKD (not receiving dialysis) when tolerated.[13]

Box A
Desired Outcomes: Goal BP for Chronic Treatment

Most patients (includes patients with clinical ASCVD [secondary prevention], diabetes, or CKD; primary prevention patients regardless of 10-year ASCVD risk score)

- <130/80 mm Hg

Older ambulatory, community-dwelling patients

- SBP <130 mm Hg

Institutionalized older patients, those with high disease burden and comorbidities, or limited life-expectancy:

- Consider a relaxed SBP goal of at least <150 mm Hg; <140 mm Hg in some patients if tolerated
- Use a team-based decision process weighing patient preferences, risks, and benefits

Historically, most patients with hypertension were treated to a goal BP of <140/90 mm Hg, with <130/80 mm Hg recommended for higher-risk patients. However, evidence demonstrates a significantly lower risk of CV events with lower BP goals. Some of the strongest data supporting the lower BP goals comes from the Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT evaluated a systolic BP goal of <120 mm Hg versus <140 mm Hg in patients with hypertension at high CV risk but without diabetes.[14] The study was stopped early after a median follow-up of 3.3 years due to a significantly lower risk of the primary composite outcome (MI, other acute coronary syndromes, stroke, HF, or death from CV causes) and all-cause mortality in patients treated to the lower BP goals. The final results when the trial was fully adjudicated were consistent with the initially published report.[15] Despite an increased risk of adverse events in the intensive treatment group (eg, hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure), the significant benefits outweighed these risks, with intensive BP control improving survival by 6 months to 3 years in middle-aged and older adults with high CV risk.[16]

In addition to SPRINT, several other systematic reviews and meta-analyses demonstrate that lower BP goals improve clinical outcomes better than higher BP goals.[17-21] In a systematic review and meta-analysis of 19 trials involving 44,989 patients, intensive treatment (mean BP 133/76 mm Hg) was associated with a reduced risk of major CV events, MI, stroke, albuminuria, and retinopathy progression compared to less intensive BP-lowering (mean BP 140/81 mm Hg).[18] The risk of serious adverse events with intensive therapy was low and did not differ significantly compared to less-intensive treatment, though severe hypotension was more frequent.

BP goal values for patients with diabetes have been a subject of debate for a number of years. A BP goal of <130/80 mm Hg was historically recommended for patients with diabetes by multiple organizations. The primary evidence supporting this recommendation was from the Hypertension Optimal Treatment (HOT) study, which compared diastolic BP goals of <90, <85, or <80 mm Hg on CV outcomes.[22] Only the subgroup of patients with diabetes (n = 1,501) had a lower risk of major CV events in the <80 mm Hg group versus the <90 mm Hg group.

However, the NHLBI-sponsored Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) study questioned the benefit of lower BP goals for patients with diabetes.[23] The ACCORD-BP was an open-label, factorial study that randomized 4,733 patients with type 2 diabetes to an SBP of <120 or <140 mm Hg. After a mean follow-up of 4.7 years, there was no significant difference in the annual rate of the primary endpoint (nonfatal MI,

nonfatal stroke, or CV death) between the two groups. However, the annual incidence of the secondary endpoint of stroke was significantly lower with the <120 mm Hg goal. Also, there are significant limitations to ACCORD-BP. First, ACCORD-BP was underpowered, as only half of the expected primary composite endpoint events occurred during the study. It was also a factorial study design. A posthoc analysis of ACCORD-BP that examined CV outcomes for participants with CVD risk factors that would have been eligible for SPRINT found similar CV event rates and adverse effect rates as seen in SPRINT.[24] Also, the evidence-based review performed for the 2017 ACC/AHA guideline found a lower risk of fatal or nonfatal stroke with lower BP goals in patients with diabetes.[17] Therefore, most patients with diabetes should be treated to a BP of <130/80 mm Hg.

Avoiding Clinical Inertia

Although hypertension is one of the most common medical conditions, BP control rates are poor. *Clinical inertia* in hypertension is defined as an office visit for which no therapeutic move was made to lower BP in a patient with uncontrolled hypertension.[25] Clinical inertia is not the entire reason why many patients with hypertension do not achieve goal BP values. However, it is a major reason that can be remedied simply through more aggressive antihypertensive drug therapy. This strategy can include initiating, titrating, or changing drug therapy.

General Approach to Treatment

All patients with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension should be engaged in lifestyle modifications. For patients with elevated blood pressure and those with stage 1 hypertension who are at low risk of ASCVD (ie, primary prevention, without CKD, without diabetes but with a 10-year ASCVD risk <10%), lifestyle modification alone is an appropriate initial treatment. The *threshold* for when these low-risk patients should start drug therapy is when the BP is ≥140/90 mm Hg with a *goal* BP of <130/80 mm Hg. For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or who have an elevated 10-year ASCVD risk ≥10% (including patients with diabetes and patients with CKD), the *threshold* for starting drug therapy is ≥130/80 mm Hg with a *goal* BP of <130/80 mm Hg.

6 The choice of initial antihypertensive drug therapy depends on the degree of BP elevation and presence of compelling indications (see Pharmacologic Therapy section). A single first-line antihypertensive drug should be started as initial therapy in most patients with newly diagnosed stage 1 hypertension. Combination drug therapy, preferably with two first-line antihypertensive drugs, should be started as initial therapy in patients with newly diagnosed hypertension presenting with more severe BP elevation (stage 2 hypertension). This general approach to initial therapy is outlined in Fig. 30-2. There are several compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with hypertension (see Fig. 30-3). Under these circumstances, the selection of antihypertensive drug therapy should follow an evidence-based order.

FIGURE 30-2

Algorithm for treatment of elevated BP and hypertension based on BP category at initial diagnosis. Drug therapy recommendations are graded with the strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendations, 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 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. *Monotherapy with an ACEi, ARB, CCB, or thiazide is appropriate in patients presenting in Stage 2 hypertension if they are at high risk for orthostatic hypertension or are very elderly.

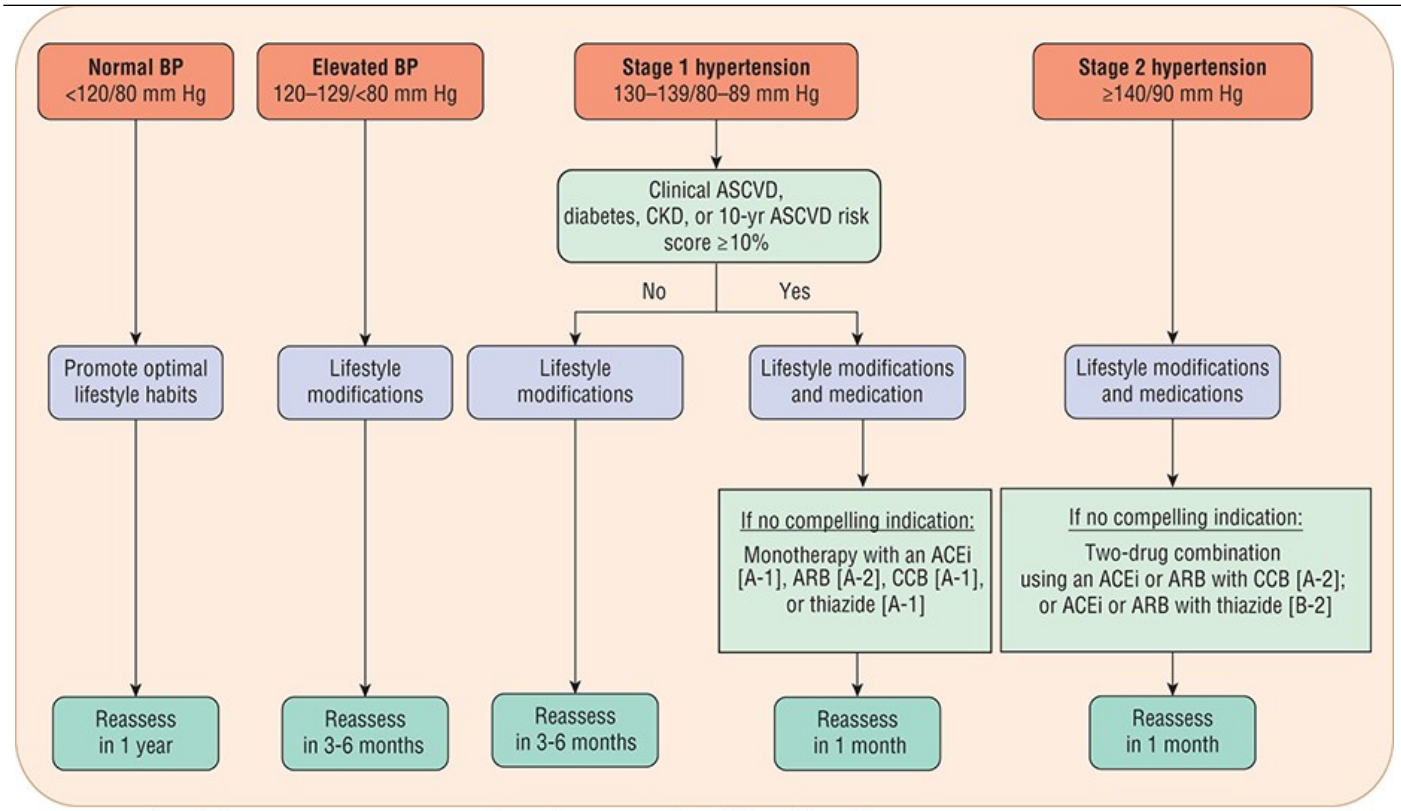
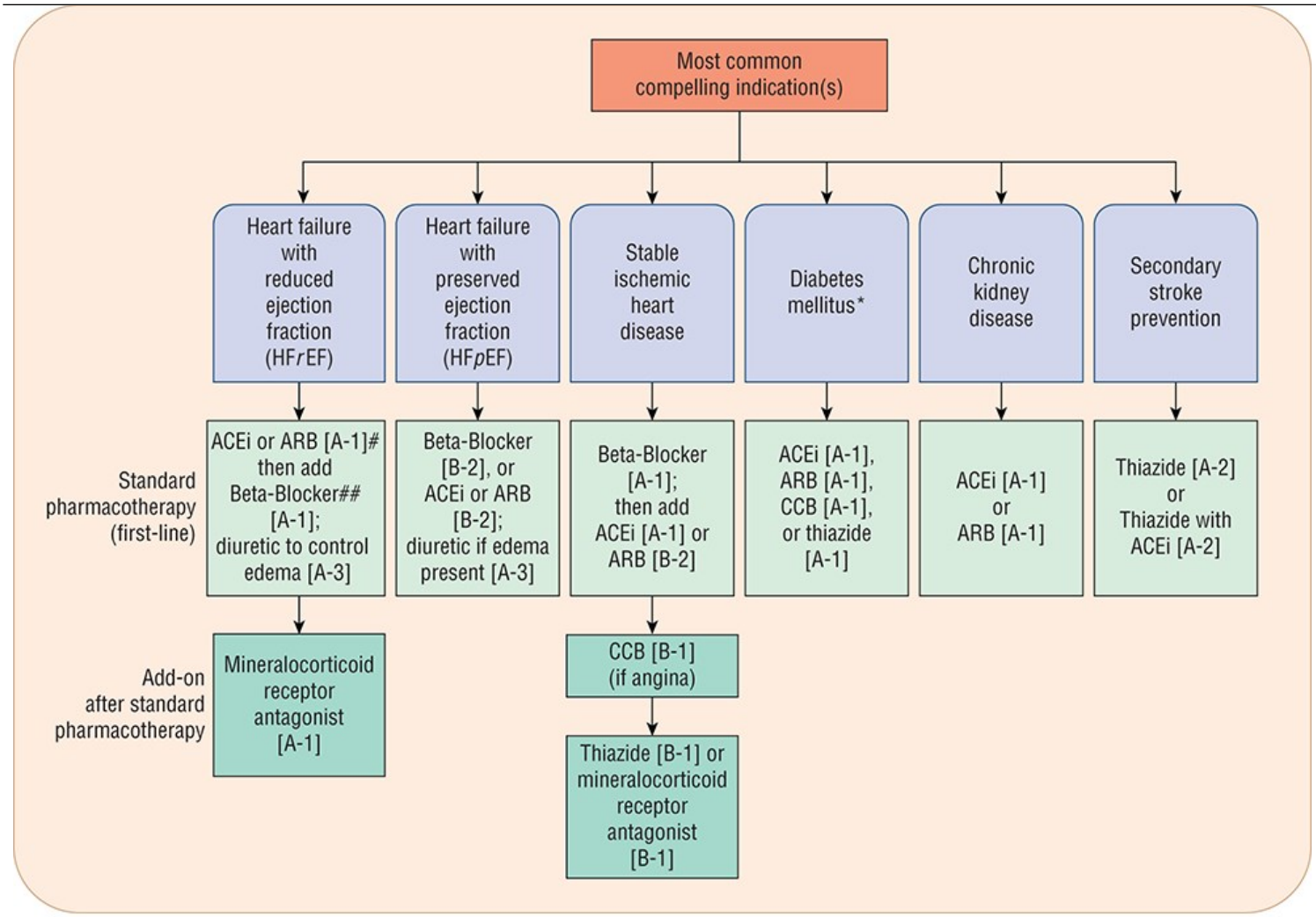


FIGURE 30-3

The most common compelling indications for individual drug classes. Compelling indications for specific drugs are evidenced-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. Add-on pharmacotherapy recommendations are when additional medications are needed to lower blood pressure to goal. Blood pressure control should be managed concurrently with the compelling indication. Drug therapy recommendations are graded with the strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendations, 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. [#]An ARB with an angiotensin receptor neprilysn inhibitor preferred ahead of an ACEi or ARB for the treatment of HFrEF.

[##]In HFrEF only, use bisprolol, carvedilol, or metoprolol succinate, titrated to the evidence-based dose.

*If albuminuria is present in diabetes, treat like chronic kidney disease and use an ACEi or ARB titrated to the maximum tolerated dose.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonpharmacologic Therapy

7 All patients with elevated blood pressure and hypertension should be prescribed lifestyle modifications. However, they should never be used to replace antihypertensive drug therapy for patients with hypertension who are not at goal BP. Recommended nonpharmacological treatments that have been shown to lower BP are listed in Table 30-4.[1] Lifestyle modifications can provide small to moderate reductions in SBP. Aside from reducing BP in patients with known hypertension, strict adherence to lifestyle modification can decrease the progression to hypertension in patients with elevated BP values, and improve other aspects of CV health (eg, cholesterol, weight).

TABLE 30-4

Lifestyle Modifications to Prevent and Manage Hypertension[a]

Modification	Recommendation	Approximate SBP Reduction (mm Hg)	
		With Hypertension	Without Hypertension
Weight loss	Maintain normal body weight (body mass index, 18.5-24.9 kg/m^2), but aim for at least ≥1 kg weight reduction. Approximate 1 mm Hg BP reduction noted per 1 kg weight loss	5	2-3
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	11	3
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride)	5-6	2-3
Physical activity	90-150 min/wk of aerobic or dynamic resistance training, and involving moderate- to-vigorous intensity[b]	• 5-8 aerobic • 4 dynamic	• 2-4 aerobic • 2 dynamic
Moderation of alcohol intake	Limit consumption to ≤2 drink equivalents per day in men and ≤1 drink equivalent per day in women and lighter-weight persons[c]	4	3

[a]Effects of implementing these modifications are time- and dose-dependent and could be greater for some patients.

[b]Aerobic exercise at 65%-75% heart rate reserve; dynamic resistance consisting of 6 exercises, 3 sets/exercise, 10 repetitions/set at 50%-80% of 1 rep maximum.

[c]One drink equivalent is equal to 1.5 oz (~45 mL) of 80-proof distilled spirits (eg, whiskey), a 5 oz (~150 mL) glass of wine (12%), or 12 oz (~350 mL) of beer.

A sensible dietary program is designed to reduce weight gradually for overweight and obese patients and restricts sodium intake with limited alcohol consumption (for patients who consume alcohol). Patients' successful implementation of dietary and lifestyle modifications requires aggressive promotion by clinicians through patient education, encouragement, and continued reinforcement. Weight loss, as little as 5% of body weight, can decrease BP significantly in overweight or obese patients. Diets rich in fruits and vegetables and low in saturated fat have been shown to lower BP in patients with hypertension.

The Dietary Approaches to Stop Hypertension (DASH) eating plan is a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. It is an evidence-based diet that lowers BP. Intake of sodium should be minimized as much as possible, ideally to 1.5 g/day, although an interim goal of a 1 g/day reduction may be reasonable considering the challenges in achieving low sodium intake. Patients should be aware of the multiple sources of dietary sodium (eg, processed foods, soups, table salt) so that they may implement the restriction. Potassium intake should be encouraged through fruits and vegetables with a high content (ideally 3,500-5,000 g/day) in those with normal kidney function or without impaired potassium excretion. Excessive alcohol use can either cause or worsen hypertension. Patients with hypertension who drink alcoholic beverages should restrict their daily intake.

Physical activity consisting of aerobic or dynamic resistance training of 90 to 150 min/week (eg, 3-4 sessions/week, lasting on average 40 min/session) and involving moderate-to-vigorous intensity should be encouraged when possible. Studies have shown that physical activity, and in particular aerobic activity, can reduce BP, even in the absence of weight loss. Patients should consult their physicians before starting an exercise program, especially

those with hypertension-associated complications.

Smoking (tobacco or other products) is not a secondary cause of essential hypertension. However, smoking is a major, independent, modifiable risk factor for CV disease. Therefore, while smoking cessation is not a recommended strategy to control BP, patients with hypertension who smoke should be counseled regarding the additional health risks that result from smoking and be encouraged to quit.

Pharmacologic Therapy

8 An ACEi, ARB, CCB, or thiazide are preferred first-line antihypertensive agents for most patients (Table 30-5).[1] These agents should be used to treat the majority of patients with hypertension because of evidence demonstrating CV event reduction. Several of these medications have subclasses where significant differences in the mechanism of action, clinical use, side effects, or evidence from outcome studies exist. β-Blocker therapy should be reserved to treat a specific, compelling indication or may be used in combination with one or more first-line antihypertensive agents for patients without a compelling indication. Other antihypertensive drug classes are considered alternative drug classes that should be limited for use in select patients after implementing first-line agents (Table 30-6).

TABLE 30-5

Most Common First-Line and Other Antihypertensive Agents

Class	Subclass	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
ACEi		Benazepril (Lotensin)	10-40	1 or 2	May cause hyperkalemia in patients with chronic kidney disease or in those receiving a potassium-sparing diuretic, or MRA; should not be used in combination with an ARB, or direct renin inhibitor; can cause acute kidney injury in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; contraindicated in pregnancy or in patients with a history of angioedema; starting dose should be reduced 50% in patients who are on a thiazide, are volume depleted, or are very elderly due to risks of hypotension.
		Captopril (Capoten)	12.5-150	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	
ARB		Azilsartan (Edarbi)	40-80	1	May cause hyperkalemia in patients with chronic kidney disease or in those receiving a potassium-sparing diuretic, or MRA; should not be used in combination with an ACEi or direct renin inhibitor; can cause acute kidney injury in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney; do not cause a dry cough
		Candesartan (Atacand)	8-32	1 or 2	
		Eprosartan (Teveten)	600-800	1 or 2	
		Irbesartan (Avapro)	150-300	1	

		Losartan (Cozaar)	50-100	1 or 2	like an ACEi may; contraindicated in pregnancy; starting dose should be reduced 50% in patients who are on a thiazide, are volume depleted, or are very elderly due to risks of hypotension.
		Telmisartan (Micardis)	20-40	1	
		Olmesartan (Benicar)	20-80	1	
		Valsartan (Diovan)	80-320	1	
Calcium channel blocker	Dihydropyridine	Amlodipine (Norvasc)	2.5-10	1	Do not use immediate-release nifedipine or immediate-release nicardipine; dihydropyridines are more potent arterial vasodilators than nondihydropyridines and may cause more peripheral edema; have additional benefits in Raynaud's syndrome.
		Felodipine (Plendil)	5-20	1	
		Nifedipine long-acting (Afeditab CR Adalat CC, Nifediac CC, Nifedical XL, Procardia XL)	30-90	1	
		Nisoldipine (Sular)	10-40	1	
	Nondihydropyridine	Diltiazem sustained release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120-480	1	Use extended-release products for hypertension; these agents block the A-V node, reduce heart rate, and may produce heart block, especially in combination with β-blockers; not all products are not AB rated as interchangeable on an equipotent milligram-per-milligram basis due to different release mechanisms and bioavailability; Cardizem LA, Matzim LA, and Verelan PM have delayed drug release for several hours after dosing and can provide chronotherapeutic drug delivery, but this does not have any clinical advantages; have additional benefits in patients with atrial tachyarrhythmia.
		Diltiazem extended release (Cardizem LA, Matzim LA)	180-480	1 (morning or evening)	
		Verapamil sustained release (Calan SR, Isoptin SR, Verelan)	180-420	1 or 2	
		Verapamil chronotherapeutic oral drug absorption system (Verelan PM)	100-400	1 (in the evening)	
Diuretic	Thiazide	Chlorthalidone (Thalitone)	12.5-25	1	Hydrochlorothiazide is a "thiazide-type" while chlorthalidone, indapamide, and metolazone are "thiazide-like." Dose in the morning to avoid nocturnal diuresis; thiazides are more effective antihypertensives than loop diuretics in most patients; use usual doses to avoid adverse metabolic effects; hydrochlorothiazide, chlorthalidone, and indapamide are preferred; chlorthalidone is approximately 1.5 times as potent as hydrochlorothiazide; have additional benefits in osteoporosis; use with caution in patients with a history of gout.
		Hydrochlorothiazide (Microzide)	12.5-50	1	
		Indapamide (Lozol)	1.25-2.5	1	
		Metolazone (Zaroxolyn)	2.5-10	1	
	Loop	Bumetanide (Bumex)	0.5-4	2	Dose in the morning and late afternoon (when twice daily) to avoid nocturnal diuresis; higher doses may be needed for patients with severely decreased glomerular filtration rate or HF; preferred over thiazides in patient with severe kidney dysfunction
		Furosemide (Lasix)	20-80	2	
		Torsemide (Demadex)	5-10	1	

					and resistant hypertension.
	Potassium-sparing	Amiloride (Midamor)	5-10	1 or 2	Weak diuretics that are used in combination with a thiazide to minimize hypokalemia; do not significantly lower BP unless used with a thiazide; should be reserved for patients experiencing diuretic-induced hypokalemia; avoid in patients with severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2); may cause hyperkalemia, especially in combination with a n MRA, ACEi, ARB, direct renin inhibitor, or potassium supplements.
		Amiloride/hydrochlorothiazide (Moduretic)	5/50	1	
		Triamterene (Dyrenium)	50-100	1 or 2	
		Triamterene/hydrochlorothiazide (Dyazide, Maxide)	37.5-75/25-50	1	
	MRA	Eplerenone (Inspra)	50-100	1 or 2	Dose in the morning and late afternoon (when twice daily) to avoid nocturnal diuresis; eplerenone contraindicated in patients with an estimated creatinine clearance <50 mL/min (0.83 mL/s), elevated serum creatinine (>1.8 mg/dL [115 µmol/L] in women, >2 mg/dL [177 µmol/L]) in men), and type 2 diabetes with albuminuria; often used as add-on therapy in resistant hypertension; avoid in patients with severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2); may cause hyperkalemia, especially in combination with an ACEi, ARB, direct renin inhibitor, or potassium supplements.
		Spironolactone (Aldactone, CaroSpir)	25-50	1 or 2	
β-Blocker	Cardioselective	Atenolol (Tenormin)	25-100	1 or 2	Abrupt discontinuation may cause rebound hypertension; have additional benefits in patients with atrial tachyarrhythmia or preoperative hypertension; in general, cardioselective agents inhibit β_1-receptors at low to moderate dose, higher doses may also block β_2-receptors (especially metoprolol); additional vasodilation with nebivolol does not result in more orthostatic hypotension; nonselective agents inhibit β_1- and β_2-receptors at all doses, can exacerbate asthma, and have additional benefits in patients with essential tremor, migraine headache, portal hypertension, and thyrotoxicosis. Agents with intrinsic sympathomimetic activity (acebutolol and pindolol) partially stimulate β-receptors while blocking against additional stimulation; no role in the management of hypertension and are contraindicated in patients with stable ischemic heart disease. Mixed α- and β-blockers produce vasodilation and have more orthostatic hypotension.
		Betaxolol (Kerlone)	5-20	1	
		Bisoprolol (Zebeta)	2.5-10	1	
		Metoprolol tartrate (Lopressor)	100-200	2	
		Metoprolol succinate extended release (Toprol XL)	50-200	1	
		Nebivolol (Bystolic)	5-20	1	
	Nonselective	Nadolol (Corgard)	40-120	1	
		Propranolol (Inderal)	160-480	2	
		Propranolol long acting (Inderal LA, Inderal XL, InnoPran XL)	80-320	1	
		Timolol (Blocadren)	10-40	1	

	Mixed α- and β-blockers	Carvedilol (Coreg)	12.5-50	2	
		Carvedilol phosphate (Coreg CR)	20-80	1	
		Labetalol (Normodyne, Trandate)	200-800	2	

TABLE 30-6

Alternative Antihypertensive Agents

Class	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency	Comments
α_1-Blocker	Doxazosin (Cardura)	1-8	1	Give first dose at bedtime; patients should rise from sitting or lying down slowly to minimize risk of orthostatic hypotension; 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, MRA; do not use in combination with an ACEi 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-agonist	Clonidine (Catapres)	0.1-0.8	2	Oral form should be avoided due to need for frequent administration and potential rebound HTN with abrupt discontinuation or nonadherence; most effective if used with a thiazide to diminish fluid retention; clonidine patch is replaced once per week
	Clonidine patch (Catapres-TTS)	0.1-0.3	1 weekly	
	Methyldopa (Aldomet)	250-1,000	2	
Direct arterial vasodilator	Minoxidil (Loniten)	10-40	1 or 2	Should be used with thiazide and β-blocker to diminish fluid retention and reflex tachycardia
	Hydralazine (Apresoline)	20-100	2 to 4	

Historical Evidence Supporting Thiazide Therapy

Landmark placebo-controlled clinical trials demonstrate that thiazide therapy irrefutably reduces the risk of CV morbidity and mortality. The Systolic Hypertension in the Elderly Program (SHEP),[6] Swedish Trial in Old Patients with Hypertension (STOP-Hypertension),[5] and Medical Research Council (MRC)[7] studies showed significant reductions in stroke, MI, all-cause CV disease, and mortality with a thiazide-based therapy versus placebo. These trials allowed for β-blockers as add-on therapy for BP control. Agents such as an ACEi, ARB, and CCB were not available at the time of these studies. However, subsequent clinical trials have compared these antihypertensive agents with a thiazide and have demonstrated similar long-term benefits.[26-32]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The results of the ALLHAT were the deciding evidence that prior guidelines used to justify thiazide therapy as first-line therapy.[26] It was designed to test the hypothesis that newer antihypertensive agents (an α-blocker, ACEi, or dihydropyridine CCB) would be superior to thiazide-based therapy. The primary objective was to compare the combined endpoint of fatal CHD and nonfatal MI. Other hypertension-related complications (eg, HF, stroke) were evaluated as secondary endpoints. This was the largest prospective hypertension trial ever conducted and included 42,418 patients aged 55 years and older with hypertension and one additional CV risk factor. This double-blind trial randomized patients to chlorthalidone-, amlodipine-, doxazosin-, or lisinopril-based therapy for a mean of 4.9 years.

The doxazosin treatment arm was terminated early when a significantly higher risk of HF versus chlorthalidone was observed.[33] The other arms were continued as scheduled, and no significant differences in the primary endpoint were seen between the chlorthalidone and lisinopril or amlodipine treatment groups at the end of the trial. However, chlorthalidone had fewer secondary endpoints than amlodipine (HF) and lisinopril (combined CV disease, HF, 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.[34] It did not prove this hypothesis. Several subgroup analyses of specific populations (eg, Black patients, CKD, diabetes) from the ALLHAT have been conducted to assess response in certain unique patient populations.[35-37] Surprisingly, none of these analyses demonstrated superior CV event reductions with lisinopril or amlodipine versus chlorthalidone. Overall, thiazides remain unsurpassed in their ability to reduce CV morbidity and mortality in most patients.

The 2017 ACC/AHA high BP guideline recommends a thiazide as first-line therapy for most patients.[1] However, an ACEi, ARB, or CCB are also comparable first-line options. Contrary to the historical preference to use a thiazide as preferred for treating most patients with hypertension, they are simply one of the four first-line drug therapy options. **Figure 30-2** displays the algorithm for treating hypertension and highlights the four first-line antihypertensive options for patients without a compelling indication for a specific drug class.

ACEi, ARB, and CCB as First-Line Agents

Clinical trial data cumulatively demonstrate that ACEi-, CCB-, or ARB-based antihypertensive therapy reduces CV events. These agents are first-line options for patients without a compelling indication. The Blood Pressure Lowering Treatment Trialists' Collaboration has evaluated the incidence of major CV events and death among different antihypertensive drug classes from 29 major randomized trials in 162,341 patients.[38] In placebo-controlled trials, major CV events were significantly lower with ACEi- and CCB-based regimens versus placebo. Although there were minor differences in the incidence of certain CV events in some comparisons, there were no differences in total major CV events when an ACEi, CCB, or thiazide was compared with each other. In studies evaluating ARB-based therapy to control regimens, the incidence of major CV events was lower with ARB-based therapy. However, the control regimens used in these comparisons included both antihypertensive drug therapies and placebo. These results were largely consistent with the network meta-analysis conducted for the 2017 ACC/AHA guideline, which found that an ACEI, ARB, CCB, or thiazide were all similar as first-line treatment for hypertension.[17]

Data from meta-analyses that incorporate high-quality randomized controlled trials provide more robust data than any single trial alone. High-quality meta-analyses are considered the highest level of evidence by the ACC/AHA guidelines and provide clinically useful data that support using ACEi-, CCB-, or ARB-based treatment for hypertension as first-line antihypertensive agents. Clinicians should use meta-analyses data as supporting evidence when selecting a first-line antihypertensive regimen for hypertension in most patients.

β-Blocker Versus First-Line Agents

9 Clinical trial data and meta-analyses cumulatively suggest that treatment with a β-blocker may reduce CV events better than placebo but not to the extent that an ACEi, ARB, CCB, or particularly thiazide diuretics do.[1] In the systematic review and network analysis conducted for the 2017 ACC/AHA guideline, β-blockers were less effective for preventing stroke and CV events than diuretics.[17]

Meta-analyses data evaluating β-blockers and their ability to reduce CV events have limitations. Most studies that were included in these analyses used atenolol as the β-blocker studied. Therefore, it is possible that atenolol is inferior and is the only β-blocker that does not reduce CV events as much as other first-line antihypertensive drug classes. A network meta-analysis comparing the effects of different β-blockers found a decreased risk of mortality and CV events with lipophilic agents (metoprolol, propranolol, and oxprenolol) compared to hydrophilic agents (atenolol).[39] However, due to challenges in the interpretation of meta-analyses of β-blockers compared to other first-line agents (eg, trials conducted at different times, use of different beta-blockers, changes in the efficacy of agents), most guideline recommendations do not differentiate between the β-blocker drug class. In the absence of a compelling indication, a β-blocker can be considered only after other first-line antihypertensive agents (ACEi or ARB, CCB, thiazide) have been used.[1,40] These findings also call into question the validity of results from prominent prospective, controlled clinical trials evaluating antihypertensive drug therapy that used β-blocker–based therapy, especially atenolol, as the primary comparator.[28,30] These studies used once-daily atenolol, which in addition to being hydrophilic, may have been inadequately dosed based on the short half-life of this agent.

β-Blocker–based antihypertensive therapy does not increase the risk of CV events; β-blocker–based therapy reduces the risk of CV events compared with no antihypertensive therapy. Using a β-blocker as a first-line antihypertensive agent is an option when an ACEi, ARB, CCB, or thiazide cannot be used. β-Blockers also have an important role as add-on therapy to first-line agents to reduce BP in patients with hypertension but without compelling indications.

Many of the clinical trials included in the meta-analyses suggest that β-blocker–based therapy may not reduce CV events as well as these other agents, used atenolol dosed once daily.[41] Atenolol has a half-life of 6 to 7 hours and is nearly always dosed once daily, while immediate-release forms of carvedilol and metoprolol have half-lives of 6 to 10 and 3 to 7 hours, respectively, and are dosed at least twice daily.[41] It is also hydrophilic, which may not penetrate the brain and cell membrane as easily as lipophilic agents, and is inferior to lipophilic agents (metoprolol, propranolol, and oxprenolol).[39] Therefore, it is possible that these findings might only apply to atenolol, particularly dosed once daily instead of twice daily. Based on available evidence, metoprolol succinate or carvedilol are the preferred β-blockers if a β-blocker is to be used.

Patients with Compelling Indications

10 Compelling indications represent specific comorbid conditions where evidence from clinical trials supports using specific antihypertensive classes to treat both the compelling indication and hypertension. Antihypertensive medication recommendations typically consist of combination drug therapy (see **Fig. 30-3**). Data from clinical trials have demonstrated a reduction in CV morbidity and/or mortality that justifies use for patients with hypertension and with such a compelling indication.

Heart Failure with Reduced Ejection Fraction

Five drug classes have compelling indications for HF with reduced ejection fraction (HFrEF), also known as systolic HF or left ventricular dysfunction.[42] The primary physiologic abnormality in HFrEF is decreased CO resulting from a decreased left ventricular ejection fraction. An evidence-based pharmacotherapy regimen for HFrEF, called *guideline-directed medical therapy*, consists of three to four drugs: an ACEi or ARB (although ARB with a neprilysin inhibitor [aka angiotensin receptor neprilysin inhibitor; ARNI] is preferred ahead of an ACEi or ARB alone according to HFrEF recommendations), an evidence-based β-blocker (ie, bisoprolol, carvedilol, metoprolol succinate) titrated to the maximum dose, and then possibly an MRA.[43] Diuretics are often needed in patients with HFrEF primarily to provide symptomatic relief of edema by inducing diuresis. Loop diuretics are often needed, especially for patients with more advanced HF and/or advanced stages of CKD. However, some patients with well-controlled HF and without significant CKD may be managed with a thiazide.

For patients with hypertension and HFrEF full implementation for guideline-directed medical therapy to treat HFrEF using multiple pharmacologic therapies should be the primary driver of pharmacotherapy. When done correctly and completely, not only are benefits related to HFrEF realized but lowering of BP to goal is usually achieved.

β-Blocker therapy modifies disease in HFrEF and is a component of standard treatment for these patients. For patients on an initial regimen of a diuretic with an ACEi or ARB (or ARNI), add-on β-blocker therapy has been shown to reduce CV morbidity and mortality.[42,44] It is of paramount importance that β-blockers be dosed appropriately due to the risk of inducing an acute exacerbation of HF. They must be started in low 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 that are proved to be beneficial in HFrEF.

After implementing a standard HFrEF regimen (diuretic, ACEi or ARB alone [or ARNI], and evidence-based β-blocker), other agents may be added to reduce CV morbidity and mortality further and reduce BP if needed. The addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone) can reduce CV morbidity and mortality in HFrEF.[44]

Heart Failure with Preserved Ejection Fraction

Approximately 50% of patients with HF have a preserved ejection fraction (HFpEF). In HFpEF, patients have signs and symptoms of HF such as dyspnea, fatigue, and possibly edema, but they have a preserved left ventricular ejection fraction (≥50%).

Unlike interventions using GDMT in HFrEF, which have been shown to decrease morbidity and mortality in HF, trials using the same antihypertensive medications in HFpEF have not shown similar benefits.[44] Therefore, treatment should be targeted at any underline symptoms, appropriate management of any underlying coronary artery disease, and attainment of goal BP to prevent progression of HF. Patients should use a β-blocker or an ACEi or ARB to treat hypertension, but if signs and symptoms of edema are present, they should receive a diuretic.[1] A mineralocorticoid receptor antagonist may be considered in patients with elevated brain natriuretic peptide concentrations or heart failure admission within one year and adequate kidney function to reduce the risk of hospitalizations.[42]

Stable Ischemic Heart Disease

Chronic stable angina and a history of acute coronary syndrome (unstable angina or acute MI) are forms of stable ischemic heart disease (aka, coronary artery disease, or coronary heart disease).[1] These are the most common forms of hypertension-associated complications. Patients with stable ischemic heart disease are at high risk for a CV event.

β-Blocker therapy has been a standard of care for treating patients with stable ischemic heart disease and hypertension for decades because they can reduce BP and improve angina symptoms by decreasing myocardial oxygen consumption and demand.[1] They also decrease cardiac adrenergic stimulation and have been shown in clinical trials to reduce the risk of a subsequent MI and sudden cardiac death. β-Blocker therapy seems to be most effective in reducing the risk of CV events in patients with recent MI and/or ischemic symptoms. While data indicate that the long-term risk of CV events and mortality may not be reduced with β-blocker therapy in patients with stable coronary artery disease (ie, do not have ischemic symptoms or have a distant history of MI),[45] β-blockers should be used for the treatment of hypertension in patients with stable ischemic heart disease.[1] An ACEi (or ARB as an alternative) has been shown to improve cardiac remodeling and cardiac function and reduce CV events in stable ischemic heart disease as an add-on to a β-blocker.

A long-acting nondihydropyridine CCB is an alternative to a β-blocker (diltiazem and verapamil) in stable ischemic heart disease.[46] The International Verapamil–Trandolapril Study (INVEST) demonstrated no difference in CV risk reduction when β-blocker-based therapy was compared with nondihydropyridine CCB-based treatment in this population.[47] Nonetheless, the preponderance of data is with β-blockers, and they remain the therapy of choice.[1,46] Importantly, the combined use of a nondihydropyridine CCB with a β-blocker should be avoided in general due to the increased risk of bradycardia.

A dihydropyridine CCB (eg, amlodipine, felodipine) is recommended as add-on therapy in stable ischemic heart disease patients who have ongoing ischemic symptoms (aka, angina or chest pain).[46] CCBs (especially nondihydropyridine CCBs) and β-blockers provide anti-ischemic effects; they lower BP and reduce myocardial oxygen demand in patients with hypertension and stable (and unstable) ischemic heart disease. Moreover, a dihydropyridine CCB can be used in combination with a β-blocker because there is not an increased risk of bradycardia. However, cardiac stimulation may occur with dihydropyridine CCBs (particularly immediate-release formulations) or β-blockers with intrinsic sympathomimetic activity (ISA), making these agents less desirable. Moreover, β-blockers with ISA should be avoided due to these deleterious effects.

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 ACEi further reduces CV events in patients with stable ischemic heart disease.[46] ARBs may provide similar benefits but have not been as extensively studied as ACEi therapy. Therefore, in stable ischemic heart disease, an ARB is generally considered an alternative to an ACEi. Thiazides can be added after that to provide additional BP lowering and to reduce CV risk further. However, thiazides do not provide anti-ischemic effects.

Diabetes Mellitus

The primary cause of mortality in patients with diabetes is CV disease, and hypertension management is an important risk reduction strategy.[1] All four first-line antihypertensive agents (ACEi, ARB, CCB, and thiazides) have been shown to reduce CV events in patients with diabetes (see **Fig. 30-3**).[1] The evidence-based review performed for the 2017 ACC/AHA guideline found no difference in all-cause mortality, CV mortality, HF, or stroke between ACEi-, ARB-, CCB-, or thiazide-based regimen in patients with diabetes.[17]

Traditionally, an ACEi or ARB was considered as a preferred antihypertensive agent for patients with diabetes. The reasons for this were that pharmacologically, ACEis and ARBs should provide nephroprotection due to vasodilation in the efferent arteriole of the kidney. Evidence from clinical studies has shown reductions in both CV risk (mostly with an ACEi) and reduction in risk of progressive kidney dysfunction (mainly with ARBs) in patients with diabetes.[13,48] However, data indicate that an ACEi or ARB does not confer significantly better CV risk reduction compared to CCBs, thiazides, or β-blockers in patients with diabetes.[48,49] In addition, the risk of kidney disease progression is low in the absence of albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g [3.4 mg/mmol]),[13,48] and many of the studies evaluating the ability of an ACEi or ARB to slow the progression of kidney dysfunction were placebo-controlled.[49] Therefore, an ACEi or ARB is recommended similarly to a CCB or thiazide in patients with diabetes and hypertension that do not have persistent albuminuria.[1]

After first-line antihypertensives (ACEi, ARB, CCB, and thiazide), a β-blocker is useful add-on therapy for BP control for patients with diabetes or to treat another compelling indication (eg, stable ischemic heart disease). A β-blocker (especially nonselective agents) can mask the signs and symptoms of hypoglycemia in patients with tightly controlled diabetes because most of the symptoms of hypoglycemia (eg, tremor, tachycardia, and palpitations) are mediated through the sympathetic nervous system. In addition, sweating, a cholinergically mediated symptom of hypoglycemia, still occurs 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 (due to endogenous epinephrine release intended to reverse hypoglycemia) may result in acutely elevated BP due to vasoconstriction. Despite these potential concerns, β-blockers can be safely used for patients with diabetes, and are recommended in patients with diabetes that also have a compelling indication (eg, stable ischemic heart disease, HF).

Based on the weight of all evidence, any first-line agent can be used for controlling hypertension for patients with diabetes in the absence of albuminuria. However, regardless of what agent is initially chosen, most patients will require combination therapy (discussed later), typically involving and ACEi or ARB with a CCB or thiazide.

Chronic Kidney Disease

Hypertension, especially uncontrolled BP, can damage the renal tissue (parenchyma) and/or the renal arteries that lead to CKD.[13] CKD in patients with hypertension initially presents as moderately increased albuminuria (urine albumin-to-creatinine ratio 30-299 mg/g [3.4-33.8 mg/mmol] 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. Patients with significant CKD (eg, GFR <60 mL/min/1.73 m^2 and/or albuminuria) have an increased risk of CV disease, and further progression to severe CKD.[1] BP control can slow the decline in kidney function and reduce the risk of a CV event in patients with CKD.

In addition to lowering BP, ACEi and ARB therapy can reduce intraglomerular pressure, which can theoretically provide additional benefits by slowing CKD progression in patients with diabetes[48] and those without diabetes.[13] It is difficult to differentiate whether the kidney protection benefits are from RAAS blockade versus BP lowering. A meta-analysis failed to demonstrate any unique long-term kidney protective effects of RAAS-blocking drugs

compared with other antihypertensive drugs, suggesting that benefits may be attributed to BP lowering.[50] 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 among patients with significant CKD.[35]

Patients may experience a rapid and profound drop in BP or acute kidney injury when initially starting an ACEi or ARB. The potential to produce acute kidney injury is particularly problematic in patients with significant bilateral renal artery stenosis or a solitary functioning kidney with stenosis. Patients with renal artery stenosis are usually older, and this condition is more common in patients with diabetes or those who smoke. Patients with renal artery stenosis do not always have evidence of kidney disease unless specific tests are performed. Starting with low dosages and evaluating serum creatinine soon after starting either an ACEi or ARB can minimize this risk.

Secondary Stroke Prevention

Ischemic stroke (not hemorrhagic stroke) and TIA are considered hypertension-associated complications. More than two-thirds of patients who have had an ischemic stroke or TIA have hypertension.[1] Achieving goal BP values in patients who have experienced an ischemic stroke is considered a primary modality to reduce the risk of recurrent stroke or TIA. A thiazide, either in combination with an ACEi or as monotherapy, is an evidence-based antihypertensive regimen for patients with a history of stroke or TIA.[1,51,52] ARB-based therapy has also been studied in this population.[53,54] Antihypertensive drug therapy should only be implemented after patients have stabilized following an acute cerebrovascular event, typically a few days after the event.[1] Moreover, the threshold for starting antihypertensive drug therapy in patients with a history of stroke is when BP is above 140/90 mm Hg.[1] Once antihypertensive therapy is initiated, these patients should be treated to a goal of <130/80 mm Hg.

Alternative Drug Treatments

It is sometimes necessary to use other antihypertensive agents such as a mineralocorticoid receptor antagonist, α-blocker, central α_2-agonist, adrenergic inhibitor, or arterial vasodilator. Although these agents effectively lower BP, they either do not have convincing evidence showing reduced morbidity and mortality in hypertension or have a high incidence of adverse effects that significantly hinder tolerability. Alternative agents are generally reserved for patients with resistant hypertension or as add-on therapy with multiple other first-line antihypertensive agents.

Special Populations

Drug therapy selection should always follow the recommendations provided by evidence-based guidelines, summarized in **Figs. 30-2** and **30-3**.[1] 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 altered. In some cases, this is because other agents have unique properties that benefit a coexisting condition but may not be based on evidence from outcome studies in hypertension.

Hypertension in Older People

Hypertension often presents as isolated systolic hypertension in older patients.[1] Epidemiologic data indicate that CV morbidity and mortality are more directly correlated to SBP than to DBP for patients aged 50 years and older. This population is also at high risk for hypertension-associated complications.[1] Although several placebo-controlled trials have specifically demonstrated risk reduction in this population, many older people with hypertension are either not treated or are treated but not at goal BP.

The SHEP was a landmark double-blind, placebo-controlled trial that evaluated chlorthalidone-based treatment for isolated systolic hypertension.[6] A 36% reduction in total stroke, a 27% reduction in coronary artery disease, and 55% reduction in HF were demonstrated versus placebo. The Systolic Hypertension in Europe (Syst-Eur) trial was another placebo-controlled trial that evaluated treatment with a long-acting dihydropyridine CCB.[8] Treatment resulted in a 42% reduction in stroke, 26% reduction in coronary artery disease, and 29% reduction in HF. These data demonstrate reductions in CV morbidity and mortality in older patients with isolated systolic hypertension, especially with thiazides and long-acting dihydropyridine CCBs.

The “very elderly” population (80 years of age and older) were underrepresented in the SHEP and Syst-Eur studies. Historically, this population was often not treated to goal either due to fear of side effects or limited evidence demonstrating benefit. However, the Hypertension in the Very Elderly Trial

(HYVET) provided definitive evidence that antihypertensive drug therapy offers significant clinical benefits in these patients.[55] The HYVET was a prospective controlled clinical trial that randomized patients 80 years and older with hypertension to placebo or antihypertensive drug therapy. It was stopped early after a median of only 1.8 years because the incidence of death was 21% higher in placebo-treated patients. Based on these results, hypertension should be treated with antihypertensive drug therapy in patients age 80 years and older.

Thiazide or β-blocker therapy has been compared with either an ACEi or CCB in older patients with systolic hypertension, diastolic hypertension, or both in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study.[56] In this trial, no significant differences in the primary CV event endpoint were seen between the thiazide-based treatment and either an ACEi or CCB. Overall, selecting a treatment that is well-tolerated and affordable may be more important than using specific antihypertensive agents in this population.

Older patients are more sensitive to volume depletion and sympathetic inhibition than younger patients. This may lead to orthostatic hypotension (see the Patients at Risk for Orthostatic Hypotension). In older patients, this can increase the risk of falls due to the associated dizziness. Therefore, centrally acting agents and α_1-blockers should generally be avoided or used with caution in older patients because they are frequently associated with dizziness and orthostatic hypotension. First-line antihypertensives provide significant benefits and can safely be used in older patients, especially those age 80 years and older, but smaller-than-usual initial doses must be used for initial therapy.

The best evidence for lower BP goals in older patients comes from the SPRINT-Senior trial, a prespecified subanalysis of patients aged 75 years and older enrolled in the SPRINT study.[57] In this cohort, older (mean age 79.9 years), community-dwelling patients without dementia and an expected life expectancy of 3 or more years who were treated to an SBP of <120 mm Hg compared an SBP of <140 mm Hg experienced a 34% reduced risk of the primary composite outcome of CVD and 33% reduced risk of all-cause mortality. While the lower SBP goal was associated with an increased risk of hypotension and electrolyte abnormalities, there was no difference in serious adverse events. The benefits of lower BP goals in older patients significantly outweighed the risk, though careful monitoring is essential to ensure safe medication use. A subsequent meta-analysis examining the risks and benefits of lower BP compared to a "relaxed" goal of <150 mm Hg found similar results.[58] Therefore, based on the totality of the evidence, older ambulatory patients should be treated to a SBP goal of <130 mm Hg.[1]

The treatment of hypertension in older patients should follow the same principles outlined for general care of hypertension. However, in patients with multiple comorbidities or disease states, or in whom the benefit of therapy may be less established (eg, nursing home resident, dementia), the risks and benefits of using a lower BP goal should be considered, taking into account patient preference and using a team-based approach. A relaxed SBP goal of <150 mm Hg (<140 mm Hg if tolerated) may be considered appropriate in these patients. Also, while the general approach to treatment is similar to younger patients, initial drug doses may be lower, and dosage titrations over a more extended period are usually needed to minimize the risk of hypotension.

Patients at Risk for Orthostatic Hypotension

11 Orthostatic hypotension is a significant drop in BP when standing and can be associated with dizziness and/or fainting. It is defined as an SBP decrease of >20 mm Hg or DBP decrease of >10 mm Hg when changing from supine to standing.[1] The risk of orthostatic hypotension is increased in older patients (especially those with isolated systolic hypotension, or those aged 80 years or older) and those with long-standing diabetes, severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and concomitant use of medications that cause venodilation (α-blockers, mixed α-/β-blockers, nitrates, and phosphodiesterase inhibitors). Interestingly, in a meta-analysis of 18,466 adults enrolled in randomized trials, intensive BP-lowering treatment was associated with a lower risk of orthostatic hypotension, possibly through improvement in long-term maladaptive mechanisms associated with high blood pressure.[59] For patients with risk factors for orthostatic hypotension, antihypertensive agents, especially a thiazide, ACEi, or ARB, should be started in low doses.

Hypertension in Children and Adolescents

Detecting hypertension in children requires customized evaluation. Hypertension is defined as SBP or DBP that is >95th percentile for sex, age, and height on at least three occasions for children.[60] BP values between the 90th and 95th percentile, or >120/80 mm Hg in adolescents, is considered elevated BP. Hypertensive children often have a family history of high BP, and many are overweight or obese, predisposing them to insulin resistance and associated CV risk. Unlike hypertension in adults, secondary hypertension is more common in children and adolescents. Therefore, an appropriate workup for secondary causes is required if elevated BP is identified. Kidney disease (eg, pyelonephritis, glomerulonephritis) is the most

common cause of secondary hypertension in children.

Nonpharmacologic treatment (eg, weight loss if overweight or obese, healthy diet, sleep, physical activity) is the cornerstone of therapy for essential hypertension in children.[60] The goal is to reduce the BP to <90th percentile for sex, age, and height and <130/80 mm Hg in adolescents aged 13 years and older.[60] An ACEi, ARB, β-blocker, CCB, and thiazide are all acceptable choices in children and have data supporting their use.[60] If an ACEi or ARB is to be used in adolescent girls of childbearing age, it is important to counsel regarding the risk of fetal injury and death since these agents are teratogenic, and an alternative antihypertensive may be considered. As with adults, the selection of initial agents should be based on the presence of compelling indications or concurrent conditions that may warrant their use.

Pregnancy

Hypertension during pregnancy is a major cause of maternal and neonatal morbidity and mortality.[1] Hypertension during pregnancy can be categorized as preeclampsia, eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension.[61] *Preeclampsia* is defined as hypertension (elevated BP ≥140/90 mm Hg on >2 occasions at least 4 hours apart after 20 weeks of gestation or ≥160/110 mm Hg confirmed within a short interval) and either proteinuria or new-onset hypertension with the onset of thrombocytopenia, impaired liver function, new-onset renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. It can lead to life-threatening complications for both mother and fetus. *Eclampsia*, the onset of convulsions in preeclampsia, is a medical emergency. Chronic hypertension is hypertension that predates pregnancy; superimposed preeclampsia is chronic hypertension associated with preeclampsia. *Gestational hypertension* is defined as new-onset hypertension arising after 20 weeks of gestation in a patient with normal BP before pregnancy that is not in the severe range (≥160/110 mm Hg), without proteinuria or other systemic findings (eg, thrombocytopenia, renal insufficiency, pulmonary edema, cerebral or visual disturbances).

It is controversial whether treating mild-to-moderate hypertension in pregnancy is beneficial. However, women with chronic hypertension before pregnancy are at increased risk of several complications, including superimposed preeclampsia, preterm delivery, fetal growth restriction or demise, placental abruption, HF, and acute kidney failure.[61,62] In an open, international, multicenter study of patients with nonproteinuric preexisting or gestational hypertension, tighter DBP goals (<85 mm Hg) was not associated with decreased rates of the primary composite outcome of pregnancy loss or high-level neonatal care compared to less-tight control (DBP <100 mm Hg).[63] However, severe hypertension (≥160/110 mm Hg) developed less often in patients randomized to the tight control group compared to less-tight control (40.6% vs 27.5%).

The treatment of severe hypertension, pre-eclampsia, and eclampsia is discussed in Chapter e31. For chronic hypertension in pregnancy, several agents may be considered (Table 30-7). Unfortunately, there are few data regarding the most appropriate therapy in pregnancy. Labetalol, long-acting nifedipine, or methyldopa are recommended as first-line agents due to their favorable safety profile.[62] Other β-blockers (not atenolol) and CCBs are also reasonable alternatives. An ACEi, ARB, and direct renin inhibitor are known teratogens and are absolutely contraindicated.

TABLE 30-7

Treatment of Chronic Hypertension in Pregnancy

Medication/Class	Comments
Methyldopa	Long-term follow-up data supports safety; considered a preferred agent
β-Blockers	Generally safe, but intrauterine growth retardation reported (mostly with atenolol)
Labetalol	Increasingly used over methyldopa because of fewer side effects; considered a first-line agent
Clonidine	Limited data available; mainly an option in the third trimester
CCB	Limited data available; no increase in major teratogenicity with exposure (except immediate-release oral nifedipine should not be used); long-acting nifedipine considered a preferred agent
Thiazide	Not first-line agents but probably safe in low doses if started prior to conception when treating essential hypertension
ACEi, ARB, direct renin inhibitor	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)

Black Patients

Hypertension affects Black patients at a disproportionately higher rate, and hypertension-associated complications are more prevalent than in other populations.[1] Reasons for these differences are not fully understood. Hypertension is also more challenging to control in Black patients and usually requires two or more antihypertensives to reach a goal of <130/80 mm Hg.[1]

BP-lowering effects of antihypertensive medication classes vary in Black patients but individual treatment response should always guide therapy, not race. CCBs and thiazides, as monotherapy, are more effective at lowering BP in Black patients and should be used first-line in the absence of a compelling indication.[1] When either of these two classes (especially thiazides) are used in combination with a β-blocker, ACEi, or ARB (which are three classes known to be less effective, on average, at lowering BP in Black patients), the antihypertensive response is increased. This may be due to the low-renin pattern of hypertension in Black patients, resulting in less BP lowering with a β-blocker, ACEi, or ARB when used as monotherapy when compared with other patient populations. Importantly, Black patients have a higher risk of angioedema from an ACEi compared with White patients, though this is not a common adverse effect.[1]

Despite potential differences in antihypertensive effects with monotherapy treatment, drug therapy selection is no different from what is recommended for the hypertensive population in general, and individual treatment response should always guide therapy, not race. Medications recommended for specific compelling indications should be used when such compelling indications are present, even if the antihypertensive effect may not be as great as with another drug class (eg, use a β-blocker first-line for hypertension in a Black patient with stable ischemic heart disease or an ACE or ARB in a Black patient with CKD).

Other Conditions

Most patients with hypertension have other coexisting conditions that may influence the selection of drug therapy. The influence of comorbid conditions should only be complementary to, and never replace, drug therapy choices recommended to treat a compelling indication. Under some circumstances, these considerations help decide 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 and another concomitant condition. These are briefly summarized in Table 30-5.

Pulmonary Disease and Peripheral Arterial Disease

β-Blockers, especially nonselective agents, have generally been avoided for patients with hypertension and reactive airway disease (asthma or chronic obstructive pulmonary disease [COPD] with a reversible obstructive component) due to a fear of inducing bronchospasm. However, cardioselective β-blockers can safely be used in patients with asthma or COPD.[1] Therefore, cardioselective β-blockers should be used to treat a compelling indication (ie, stable ischemic heart disease or HF) for patients with reactive airway disease.

PAD is a non-coronary form of ASCVD. Patients with PAD are at an increased risk of stroke and CV events.[1,64] While β-blockers can theoretically be problematic for patients with PAD due to possible decreased peripheral blood flow secondary to unopposed stimulation of α_1-receptors that results in vasoconstriction, available data indicate that β-blockers do not worsen claudication symptoms or cause functional impairment.[64] Antihypertensive treatment for patients with PAD should follow the same general principles as patients without PAD.[1]

Metabolic Syndrome

Metabolic syndrome is a cluster of multiple cardiometabolic risk factors.[1] It has been defined as the presence of three of the following five criteria: abdominal obesity, elevated triglycerides, low HDL cholesterol, elevated BP (or receiving drug treatment for high BP), and elevated fasting blood glucose.[65] It is widely accepted that patients with metabolic syndrome are at increased risk of developing CV disease and/or type 2 diabetes. The cornerstone of treatment involves lifestyle modification (eg, weight loss if overweight or obese, exercise, dietary modifications). There is no definitive evidence that any first-line antihypertensive medication class is better or worse than another in reducing CV events in patients with metabolic syndrome.[1] While thiazides have been associated with a slight increase in blood glucose and faster progression to diabetes, a subgroup analysis of ALLHAT found that CV events were reduced more with chlorthalidone when compared to lisinopril in patients with impaired fasting glucose.[36] Therefore, any first-line antihypertensive can be used for patients with metabolic syndrome.

Erectile Dysfunction

Most antihypertensive agents, particularly β-blockers and mineralocorticoid receptor antagonists, have been 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 rather a symptom of underlying vascular disease. β-Blockers have historically been labeled as agents that cause significant sexual dysfunction. However, evidence supporting this notion is limited. A systematic review of 15 studies involving 35,000 patients assessing β-blocker use for MI, HF, and hypertension found only a slight increased risk for erectile dysfunction.[66] In addition, prospective long-term data from the Treatment of Mild Hypertension Study (TOMHS) and the Veterans Administration Cooperative trial show no difference in the incidence of erectile dysfunction between thiazide and β-blocker versus an ACEi and CCB.[67,68] Centrally acting agents are associated with higher rates of sexual dysfunction and should be avoided in men with erectile dysfunction.

Hypertensive men frequently have ASCVD, which frequently results in erectile dysfunction. Therefore, erectile dysfunction is 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.

Resistant Hypertension

12 Resistant hypertension is defined as failure to achieve goal BP using three or more antihypertensive drugs with complementary mechanisms of action (ideally using optimal doses, one of which is a diuretic) or when four or more antihypertensive drugs are needed to achieve BP control.[1,69] Approximately 12% to 15% of patients with hypertension have apparent treatment-resistant hypertension.[69] Patients with newly diagnosed hypertension or who are not receiving drug therapy should not be considered to have resistant hypertension. Difficult-to-control hypertension is persistently elevated BP despite treatment with two or three drugs, which fails to meet the criteria for resistant hypertension.

Several causes of resistant hypertension are listed in Table 30-8. Volume overload is a common cause, thus highlighting the importance of diuretic therapy in managing hypertension. Pseudoresistance should also be ruled out by assuring adherence to prescribed therapy and possibly using home BP measurements (using a self-monitoring device or 24-hour ABP monitor).[1] Patients should be closely evaluated to see if any of these causes can be

reversed.

TABLE 30-8

Causes of Resistant Hypertension

Improper BP 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 30-1

Associated conditions:

- Obesity
- Excess alcohol intake
- Obstructive sleep apnea

Secondary hypertension

Treatment of patients with resistant hypertension should ultimately follow the principle of drug therapy selection from the 2017 ACC/AHA guideline. Compelling indications, if present, should guide selection assuming that these patients are on a thiazide or other type of diuretic. However, there are treatment philosophies that are germane to the management of resistant hypertension: (a) assuring adequate diuretic therapy, (b) appropriate use of combination therapy, and (c) using alternative antihypertensive agents when needed.

Assuring Appropriate Diuretic Therapy

Diuretics have a prominent role in the pharmacotherapy of resistant hypertension. Thiazides are first-line antihypertensive agents, but chlorthalidone (thiazide-like) is recommended ahead of hydrochlorothiazide for patients with resistant hypertension because it is more potent on a milligram-per-milligram basis.[69] Though less commonly used, indapamide (similar to chlorthalidone as "thiazide-like") is also a more potent antihypertensive agent than hydrochlorothiazide at commonly prescribed doses, and the evidence does not demonstrate a higher risk of metabolic side effects.[70]

A mineralocorticoid receptor antagonist (eg, spironolactone) is a highly effective add-on agent.[1,69] Data indicate that many patients with resistant hypertension have some degree of underlying hyperaldosteronism, justifying the role of adding a mineralocorticoid receptor antagonist. Spironolactone has been compared to an α-blocker and a β-blocker as add-on therapy for resistant hypertension in the PATHWAY-2 study.[71] The BP-lowering effect of spironolactone was approximately double that of doxazosin and bisoprolol, reinforcing the benefits of blocking aldosterone by using a mineralocorticoid receptor antagonist in managing resistant hypertension.

Clinicians may consider using a loop diuretic, even in place of a thiazide, for patients with resistant hypertension who have compromised kidney function (eg, estimated GFR <15 mL/min/1.73 m^2).[1,69] When a loop diuretic is used, a long-acting agent such as torsemide, which can be dosed once daily, should be used over shorter-acting agents such as furosemide and bumetanide, which may need to be dosed multiple times a day.[69]

First-Line Antihypertensive Agents

Angiotensin-Converting Enzyme Inhibitors (ACEi)

An ACEi is a first-line therapy option in most patients with hypertension.[1] The ALLHAT demonstrated less HF and stroke with chlorthalidone versus

lisinopril,[26] while another outcome study showed similar, if not better, outcomes with an ACEi versus hydrochlorothiazide.[32] It is possible that the different thiazides have different abilities to reduce CV events. Nonetheless, strong evidence demonstrates that ACEi therapy overall reduces CV events comparably to other first-line antihypertensive agents.

ACE facilitates the production of angiotensin II that has a major role in arterial BP regulation, as depicted in **Fig. 30-1**. ACE is distributed in many tissues and is present in several different cell types, but its main location is endothelial cells. Therefore, the primary site for angiotensin II production is in the blood vessels, not the kidney. An ACEi blocks the ACE, thus inhibiting the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor that 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.

An ACEi also blocks the degradation of bradykinin and stimulates the synthesis of other vasodilating substances (prostaglandin E_2 and prostacyclin). Because an ACEi lowers BP in patients with normal plasma renin activity, bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of an ACEi, and is also responsible for the side effect of a dry cough. An ACEi may effectively prevent or regress LVH by reducing direct stimulation of angiotensin II on myocardial cells.

There are many evidence-based indications for an ACEi (see **Fig. 30-3**). An ACEi reduces CV morbidity and mortality in patients with HFrEF and decreases the progression of CKD. An ACEi is a first-line option for patients with diabetes and hypertension because of demonstrated CV disease and kidney benefits. A two-drug regimen of an ACEi with a thiazide is first-line in recurrent stroke prevention based on benefits demonstrated from the PROGRESS trial showing a reduced risk of secondary stroke.[31] As an add-on to β-blocker therapy, evidence indicates that an ACEi further reduces CV risk in patients with stable ischemic heart disease.[46,72-74]

Most ACEi medications can be dosed once daily for hypertension (**Table 30-5**). 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.

ACEi therapy is generally well tolerated. Because they decrease aldosterone, an increase in potassium serum concentrations can occur. While this increase is usually small, hyperkalemia is possible. Patients with CKD or taking other agents which may increase potassium (eg, potassium supplements, potassium-sparing diuretics, mineralocorticoid receptor antagonists) are at the highest risk for hyperkalemia. Judicious monitoring of serum potassium and creatinine values within 4 weeks of starting or increasing the dose of an ACEi can often identify abnormalities early before they evolve into serious adverse events.

The most worrisome adverse effect of ACEi therapy is acute kidney injury. This serious adverse effect is uncommon, and the development of severe acute kidney failure is rare, occurring in less than 1% of patients. Preexisting kidney disease increases the risk of this side effect. Severe bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders 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 injury from an ACEi. Slow titration of the ACEi dose and judicious kidney function monitoring can minimize risk and allow early detection of patients with renal artery stenosis.

GFR does decrease somewhat in patients when started on an ACEi.[1] 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 newly started on an ACEi. Either modest elevations of ≤35% (for baseline creatinine values ≤3 mg/dL [265 µmol/L]) or absolute increases <1 mg/dL (88 µmol/L) do not warrant changes. If larger increases occur, ACEi therapy should be stopped or the dose reduced.

Angioedema is a serious potential complication of ACEi therapy. It occurs in <1% of the population and is more likely in Black patients and smokers. Symptoms include lip and tongue swelling and possibly difficulty breathing. All patients with ACEi-induced angioedema should have ACEi therapy stopped. However, angioedema associated with laryngeal edema and/or pulmonary symptoms occasionally occurs and requires additional treatment with a bradykinin-2 receptor antagonist (eg, icatibant), fresh frozen plasma, and/or emergent intubations to support respiration. Even if not from an ACEi, a history of angioedema precludes the use of an ACEi (it is a contraindication). Cross-reactivity between an ACEi and an ARB does not appear to be a significant concern. The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial enrolled 75 patients with a history of ACEi-induced angioedema and randomized these patients to either placebo or ARB therapy.[75] There were no cases of repeat angioedema among these patients. These data suggest that the cross-reactivity is low. Hence, an ARB can be used in a patient with a history of ACEi-induced angioedema when needed. However, clinicians should monitor for repeat occurrences since idiopathic angioedema may still occur.

A persistent dry cough may develop in up to 20% of patients treated with an ACEi. The inhibition of bradykinin breakdown pharmacologically explains it. This cough does not cause pulmonary disease but is annoying and can compromise adherence. It should be differentiated from a “wet” cough due to pulmonary edema, which may be a sign of uncontrolled HF and not an ACEi-induced cough.

An ACEi (and ARB or direct renin inhibitor) is absolutely contraindicated in pregnancy. Female patients of childbearing age should be counseled regarding effective birth control as ACEi therapy are fetotoxic.[1] Fetopathy (group of conditions that includes renal failure, renal dysplasia, hypotension, oligohydramnios, pulmonary hypotension, hypocalvaria, and death) has occurred with ACEi exposure in the second and third trimesters. Similar to a thiazide, an ACEi can increase lithium serum concentrations in patients on lithium therapy. Concurrent use of an ACEi with a potassium-sparing diuretic, potassium supplements, or mineralocorticoid receptor antagonist may result in hyperkalemia. An ACEi should not be used with an ARB or direct renin inhibitor to avoid possible hyperkalemia.

Lower than normal starting doses of an ACEi should be used for patients at risk for orthostatic hypotension or severe renal dysfunction (eg, elderly patients, those with CKD). Acute hypotension may occur at the onset of ACEi therapy. Patients who are sodium or volume-depleted, in an HF exacerbation, very elderly, or on concurrent vasodilators or thiazide therapy are at high risk for this effect. It is important to start with half the usual dose of an ACEi for all patients with these risk factors and use slow dose titration.

Angiotensin Receptor Blockers (ARBs)

Two enzymatic pathways generate angiotensin II: the RAAS, which involves ACE, and an alternative path that uses other enzymes such as chymase (aka “tissue ACE”). An ACEi inhibits 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.

ARB therapy directly blocks the AT_1 receptor, which 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. They do not block the AT_2 receptor. Therefore, the beneficial effects of AT_2 receptor stimulation (vasodilation, tissue repair, and inhibition of cell growth) remain intact with ARB use. Unlike an ACEi, an ARB does not block the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin (eg, vasodilation) are not present with ARB therapy.

An ARB is a first-line therapy option in most patients with hypertension.[1] ARB therapy has been directly compared with ACEi therapy in patients with high CV risk.[76] The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ON-TARGET) was a double-blind trial that randomized 25,620 patients (69% with a history of hypertension-based historical standards, mean BP of 142/82 mm Hg) to ACEi-based therapy, ARB-based therapy, or the combination of an ACEi with an ARB. After a median follow-up of 56 months, there was no difference in the primary endpoint (CV death or hospitalization for HF) between any of the three treatment groups. Therefore, these data establish that the CV event–lowering benefits of ARB therapy is similar to ACEi therapy. Moreover, the combination of an ACEi with an ARB had no additional benefits on CV events and was associated with a higher risk of side effects (renal dysfunction, hypotension, hyperkalemia). Therefore, concurrent use of an ACEi with an ARB for the management of hypertension is not recommended.[1]

For patients with type 2 diabetes and CKD, the progression of kidney disease is significantly reduced with ARB therapy.[48] Some benefits are independent of BP lowering, suggesting that the pharmacologic effects of ARBs on the efferent arteriole may result in attenuated progression of kidney disease. For patients with HFrEF, ARB therapy has been shown to reduce the risk of hospitalization for HF when used as an alternative therapy in ACEi-intolerant patients.[44]

ARBs have been compared head-to-head with CCBs. The Morbidity and Mortality After Stroke: Eprosartan Versus Nitrendipine in Secondary Prevention (MOSES) trial demonstrated that eprosartan reduced the risk of recurrent stroke greater than nitrendipine in patients with a past medical history of cerebrovascular disease.[53] These data support the common notion that ARBs may have cerebroprotective effects that may explain CV event reductions. Another outcome study, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) 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.[30] However, the occurrence of certain components of the primary endpoint (stroke and MI) 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 endpoint.

The addition of a CCB or thiazide to an ARB significantly increases antihypertensive efficacy. Similar to an ACEi, 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.

ARB therapy has the lowest incidence of side effects compared with other antihypertensive agents.[77] ARBs do not affect bradykinin and do not elicit a dry cough like an ACEi. While referred to as an "ACEi without a cough," pharmacologic differences between an ARB and ACEi highlight that they could have different effects on vascular smooth muscle and myocardial tissue that can correlate to different effects. Regardless, they are first-line options for hypertension, and they are reasonable alternatives for patients who do not tolerate ACEi therapy because of a cough. Due to their excellent tolerability, safety profile, and generic availability, ARBs are increasingly preferred by clinicians over an ACEi for hypertension.

An ARB may cause renal insufficiency, hyperkalemia, and orthostatic hypotension in a manner identical to that of an ACEi. The same precautions that apply to ACEi therapy regarding suspected bilateral renal artery stenosis, concomitant medications that can raise potassium, and/or increase the risk of hypotension apply to ARBs. As previously discussed, patients with a history of ACEi angioedema can be treated with an ARB when needed.[78] An ARB should never be used in pregnancy. An ARB should not be used with an ACEi or direct renin inhibitor.

Calcium Channel Blockers (CCB)

Both dihydropyridine CCBs and nondihydropyridine CCBs are first-line therapies for hypertension.[1] CCBs also have compelling indications in stable ischemic heart disease as an add-on to a β-blocker, while a nondihydropyridine CCB should be used as an alternative to a β-blocker. However, they are primarily used as add-on therapy to other antihypertensive drug classes with this compelling indication.

Contraction of cardiac and smooth muscle cells requires increased free intracellular calcium concentrations from the extracellular fluid. When the 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 the 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). Available CCBs only block the L-type channel, which leads to coronary and peripheral vasodilation.

The two subclasses, dihydropyridines and nondihydropyridines (see **Table 30-5**), are pharmacologically different from each other. While their antihypertensive effectiveness is similar, they differ somewhat in other pharmacodynamic effects. Nondihydropyridines (verapamil and diltiazem) decrease heart rate and slow atrioventricular nodal conduction. Similar to a β-blocker, these drugs may also treat supraventricular tachyarrhythmias (eg, atrial fibrillation). Verapamil (and diltiazem to a lesser extent) produces negative inotropic and chronotropic effects that are responsible for its propensity to precipitate or cause systolic HF in high-risk patients. 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 is more pronounced with the first-generation dihydropyridines (eg, nifedipine) and is significantly diminished with the newer agents (eg, 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.

Dihydropyridine CCBs have been extensively studied in hypertension and are the primary agents used for this indication. In ALLHAT, there was no difference in the primary outcome between chlorthalidone and amlodipine, and only the secondary outcome of HF was higher with amlodipine.[26] A subgroup analysis of ALLHAT directly compared amlodipine with lisinopril and demonstrated that there was no difference in the primary outcome.[79] However, amlodipine was superior to lisinopril for BP control in Black patients, and for stroke reduction in Black patients and women. As discussed previously, the VALUE study also showed no difference between valsartan and amlodipine in the primary outcome of the first CV event in high-risk patients.[30]

Dihydropyridine CCBs are effective in older patients with isolated systolic hypertension. The placebo-controlled Syst-Eur trial demonstrated that a long-acting dihydropyridine CCB reduced the risk of CV events markedly in isolated systolic hypertension.[8] A long-acting dihydropyridine CCB, similar to a thiazide, should be strongly considered as preferred therapy in a patient with isolated systolic hypertension and no other compelling indications.

Among dihydropyridine CCBs, 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 reflex sympathetic stimulation and is likely avoided by using sustained-release formulations of nifedipine. For this reason, all other dihydropyridines have an intrinsically long half-life or are sustained-release formulations. Immediate-release nifedipine has been associated with an increased incidence of adverse CV effects, is not approved for the treatment of hypertension, and should never be used to treat hypertension. Other side effects of dihydropyridine CCBs include dizziness, flushing, headache, gingival hyperplasia, peripheral edema, mood changes, and various GI complaints. Side effects due to vasodilation such as dizziness, flushing, headache, and peripheral edema occur more frequently with all dihydropyridine CCBs than with the nondihydropyridine CCBs because they are less potent vasodilators.

Diltiazem and verapamil are nondihydropyridine CCBs that can cause cardiac conduction abnormalities such as bradycardia or atrioventricular block. These problems occur mainly with high doses or when used for patients with preexisting cardiac conduction abnormalities. HF has been reported in otherwise healthy patients due to negative inotropic effects. Both drugs can cause peripheral edema and hypotension. Verapamil causes constipation in some patients. This side effect also occurs with diltiazem, but to a lesser extent.

Verapamil and diltiazem are moderate cytochrome P450 3A4 isoenzyme system inhibitors and can cause drug-drug interactions that result in increased serum concentrations of other drugs metabolized by this isoenzyme system (eg, cyclosporine, digoxin, lovastatin, simvastatin, tacrolimus, theophylline). The use of verapamil or diltiazem with a β-blocker should be avoided for the treatment of hypertension 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 the 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 (eg, ≥1 quart daily).

Many different formulations of verapamil and diltiazem are currently available (see **Table 30-5**). Although certain individual sustained-release verapamil and diltiazem products contain the same active drug, they are usually not AB-rated by the FDA as interchangeable on a milligram-per-milligram basis due to different biopharmaceutical release mechanisms. However, the clinical significance of these differences is likely negligible.

Thiazides and Other Diuretics

There are four subclasses of diuretics: thiazides, loops, potassium-sparing agents, and mineralocorticoid receptor antagonists (see Table 30-5).[1,80] A thiazide is the preferred diuretic for hypertension and is considered a first-line therapy option in most patients.[1] The best available evidence justifying this recommendation is from the ALLHAT.[26] Moreover, when combination therapy is needed in hypertension to control BP, a thiazide as an add-on agent, but not necessarily the second agent, is effective in augmenting BP lowering.

Loop diuretics are more potent agents for inducing diuresis but are not ideal antihypertensives unless treating edema is also needed. In general, loop diuretics are sometimes required over a thiazide for hypertension in patients with severe CKD when estimated GFR is <30 mL/min/1.73m^2, especially in the case of hydrochlorothiazide or when edema is present.[69] However, many patients with an estimated GFR between 25 and 30 mL/min/1.73m^2, but not on dialysis, will still have antihypertensive effects with thiazides. This is especially true with chlorthalidone.[69]

Potassium-sparing diuretics are weak antihypertensive agents when used alone and do not enhance antihypertensive effects when combined with a thiazide or loop diuretic. Their use in hypertension is in combination with another diuretic to counteract the potassium-wasting properties of the other diuretic agent.

Mineralocorticoid receptor antagonists (MRAs; spironolactone and eplerenone) inhibit aldosterone activity and are sometimes considered potassium-sparing diuretics. However, they are more potent as antihypertensives and should be viewed as an independent class due to evidence supporting different compelling indications. Mineralocorticoid receptor antagonists are most commonly used to treat resistant hypertension, as elevated aldosterone concentrations are prevalent in this setting. They are also used as an add-on agent in patients with HF, with or without concomitant hypertension.

The exact antihypertensive mechanism of action of non-MRA diuretics is not completely known but has been well hypothesized. The drop in BP seen when they are first started is caused by an initial diuresis. Diuresis causes reductions in plasma and stroke volume, which decreases CO and BP. This initial drop in CO causes a compensatory increase in PVR. With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values. However, PVR decreases to values that are lower than the pretreatment baseline. This reduction in PVR is responsible for persistent antihypertensive effects.

With thiazides, additional actions may further explain their antihypertensive effects. They mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by the excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood, and PVR 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.

Diuretics should be dosed in the morning when given once daily and in the morning and late afternoon when dosed twice daily to minimize nocturnal diuresis. However, with chronic use, thiazides, potassium-sparing diuretics, and MRAs rarely cause a pronounced diuresis.

The major pharmacokinetic differences between the different thiazide medications 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, to a greater extent, chlorthalidone are the two most frequently used thiazides in landmark clinical trials that have demonstrated reduced morbidity and mortality. Hydrochlorothiazide is considered a “thiazide-type” agent, while chlorthalidone is a “thiazide-like” agent. These agents are not equipotent on a milligram-per-milligram basis; chlorthalidone is 1.5 to 2 times more potent than hydrochlorothiazide.[80] This is likely attributed to a longer half-life (45-60 hours vs 8-15 hours) and a longer duration of effect (48-72 hours vs 16-24 hours) with chlorthalidone.

Thiazides are effective in lowering BP, especially when used in combination with most other antihypertensives. Two independent pharmacodynamic effects explain this additive response. 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, ACEi, or ARB is indicated in a Black patient but does not elicit sufficient antihypertensive effect. Adding a thiazide, similar to a CCB, 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 thiazide.

Side effects of a thiazide 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 (eg, hydrochlorothiazide up to 200 mg/day). Current guidelines recommend dosing hydrochlorothiazide up to 50 mg/day or chlorthalidone up 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 even less significant, hypokalemia is more pronounced, 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. Low-dose therapy (ie, 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) causes less electrolyte disturbances than higher doses. However, because the most effective doses of these two thiazides are hydrochlorothiazide 50 mg daily and chlorthalidone 25 mg daily, efforts should be made to keep potassium in the therapeutic range by careful monitoring, especially when higher doses are used.

Thiazide-induced hyperuricemia can precipitate gout. This side effect may be especially problematic for patients with a previous history of gout and is more common with thiazides. However, acute gout is unlikely in patients with no prior history of gout. If gout occurs in a patient who requires thiazide therapy, allopurinol can be given to prevent gout and not compromise thiazide’s antihypertensive effects. High doses of thiazide and loop diuretics may increase fasting glucose and serum cholesterol values. These effects, however, usually are transient and often inconsequential.[80]

Potassium-sparing diuretics can cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with an MRA, ACEi, ARB, direct renin inhibitor, or potassium supplements. Hyperkalemia is especially problematic for the MRA eplerenone, a selective antagonist of aldosterone. Due to this increased risk of hyperkalemia, eplerenone is contraindicated for patients with impaired kidney function or type 2 diabetes with proteinuria (see **Table 30-5**). While spironolactone may cause gynecomastia in up to 10% of patients, this rarely occurs with eplerenone.

A thiazide can be used safely with most other agents. However, concurrent administration with lithium may increase lithium serum concentrations and predispose patients to lithium toxicity.

β-Blockers

β-Blockers have been used in several large outcome trials in hypertension. However, in most of these trials, a thiazide was the first-line agent with a β-

blocker added for additional BP lowering. For patients with hypertension but without compelling indications, a β-blocker should not be used as the initial first-line agent. This recommendation is based on meta-analyses 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 who do not have a compelling indication for a β-blocker.[1]

A β-blocker is only an appropriate first-line agent in hypertension when treating specific, compelling indications (eg, stable ischemic heart disease, HF). Numerous trials have shown a reduced risk of CV events when β-blockers are used following an MI, during an acute coronary syndrome, or in patients with chronic stable angina with ischemic symptoms. Although once contraindicated in HF, studies have shown that bisoprolol, carvedilol, and metoprolol succinate reduce mortality in patients with HFrEF who are treated with a diuretic and ACEi.

Several mechanisms of action have been proposed for β-blockers, but none alone has been consistently associated with reducing arterial BP. β-Blocker therapy has negative chronotropic and inotropic effects that reduce CO, which explains some of the antihypertensive effects. However, CO falls equally for patients treated with a β-blocker regardless of BP lowering. Additionally, β-blockers with ISA do not reduce CO, yet they lower BP and decrease peripheral resistance. However, β-blockers with ISA are contraindicated in stable ischemic heart disease because they stimulate β-receptors.

β-adrenoceptors are also located on the surface membranes of juxtaglomerular cells, and a β-blocker inhibits these receptors and thus the release of renin. However, there is a weak association between plasma renin and the antihypertensive efficacy of β-blocker therapy. Some patients with low plasma renin concentrations do respond to β-blocker treatment. Therefore, additional mechanisms likely also account for the antihypertensive effect of a β-blocker.

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

β_1-adrenoceptors and β_2-adrenoceptors are distributed throughout the body, but they concentrate differently in specific 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. A cardioselective β-blocker is not likely to provoke bronchospasm and vasoconstriction. β_2-Receptors mediate insulin secretion and glycogenolysis. Blocking β_2-receptors may reduce these processes and increase blood glucose or blunt recovery from hypoglycemia.

Cardioselective β-blockers (eg, bisoprolol, metoprolol, nebivolol) have clinically significant advantages over nonselective agents (eg, propranolol, nadolol) and are preferred when using a β-blocker to treat hypertension. Cardioselective agents are safer than nonselective agents for patients with asthma or diabetes who have a compelling indication for a β-blocker. However, cardioselectivity is a dose-dependent phenomenon; at higher doses, some 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 and may not occur with highly selective β-blockers (eg, bisoprolol).

Some β-blockers (eg, 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 the sympathetic tone is low, as it is during resting states, β-receptors are partially stimulated by ISA β-blockers. Therefore, resting heart rate, CO, and peripheral blood flow are not reduced when these types of β-blockers are used. Theoretically, ISA agents have advantages over non-ISA β-blockers in certain patients with HF or sinus bradycardia. Unfortunately, they do not reduce CV events as well as other β-blockers. In fact, they may increase CV risk in patients with stable ischemic heart disease. Thus, agents with ISA are rarely needed and have no role in the management of hypertension.

Pharmacokinetic differences among β-blockers relate to first-pass metabolism, route of elimination, the 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 are renally excreted. The dose of these agents may need to be reduced for patients with moderate-to-severe CKD.

β-blockers, especially those with high lipophilic properties, penetrate the central nervous system and may cause other effects. Propranolol is the most lipophilic. It is thought that higher lipophilicity is associated with more central nervous system side effects (dizziness, drowsiness). However, the lipophilic properties 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.

Most side effects of β-blockers are extensions of their ability to antagonize β-adrenoceptors. β-blockade in the myocardium can be associated with bradycardia, atrioventricular conduction abnormalities (eg, second- or third-degree heart block), and the development of acute HF. The decrease in heart rate may benefit certain patients with atrial arrhythmias (atrial fibrillation, atrial flutter) and hypertension by both providing rate control and BP lowering. β-blocker therapy usually only produces HF if used in high initial doses for patients with preexisting left ventricular dysfunction or if started in these patients during an acute HF exacerbation. Blocking β_2-receptors in arteriolar smooth muscle may cause cold extremities and may aggravate intermittent claudication or Raynaud's phenomenon due to decreased peripheral blood flow. Also, there is an increase of sympathetic tone during periods of hypoglycemia in patients with diabetes that may result in a significant increase in BP because of unopposed α-receptor-mediated vasoconstriction.

Abrupt cessation of β-blocker therapy can cause harm. Abrupt cessation may lead to rebound hypertension (a sudden increase in BP to or above pretreatment values). Cardiac ischemia (aka, angina, or chest pain), a CV event, or even death in patients with coronary artery disease can also result from abrupt cessation. 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 the progression of underlying coronary disease, hypersensitivity of β-adrenergic receptors due to upregulation, and increased physical activity after withdrawal of a drug that decreases myocardial oxygen requirements. For patients without coronary disease, abrupt discontinuation may present as tachycardia, sweating, and generalized malaise in addition to increased BP.

Like a thiazide, β-blocker therapy has been shown to increase serum cholesterol and glucose values, but these effects are transient and of little-to-no clinical significance. For patients with diabetes, the reduction in CV events was as great with β-blocker therapy as with an ACEi in the United Kingdom Prospective Diabetes Study (UKPDS)[81] and far superior to placebo in the SHEP trial.[6] In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, patients with diabetes and hypertension who were randomized to metoprolol tartrate had a small increase in hemoglobin A1C values, while patients randomized to carvedilol did not.[82] This suggests that mixed α- and β-blocking effects of carvedilol may be preferential to metoprolol for patients with uncontrolled diabetes.

Nebivolol is a third-generation β-blocker. Similar to carvedilol and labetalol, this β-blocker results in vasodilation. However, carvedilol and labetalol cause vasodilation because of their ability to block α_1-receptors, while nebivolol causes vasodilation through the release of nitric oxide. There are no proven long-term clinical benefits of the nitric oxide effects seen with nebivolol, but this might explain a lower risk of β-blocker–associated fatigue, erectile dysfunction, and metabolic side effects (eg, hyperglycemia) with this agent.

Alternative Agents

13 Alternative antihypertensive agents may be used as add-on therapy to provide additional BP lowering in patients who are already treated with combination therapy consisting of first-line antihypertensives.

α_1-Blocker

Selective α_1-receptor blockers (doxazosin, prazosin, and doxazosin) 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 more secondary endpoints of stroke, HF, and CV events were seen with doxazosin than chlorthalidone.[33] These data demonstrated that thiazides are superior to α_1-blockers in preventing CV events in patients with hypertension. Therefore, α_1-blockers should only be used in combination with first-line antihypertensive agents.

An α_1-blocker 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 first-line antihypertensive agents.

A potentially severe side effect of an α_1-blocker is a "first-dose" phenomenon 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 a dose increase. These episodes are accompanied by orthostatic hypotension and can be mitigated by taking the first dose and subsequent first increased doses at bedtime. Because orthostatic

hypotension and dizziness often persist with chronic administration, these agents should be used cautiously in older patients that are at an increased risk of falls. Sodium and water retention can occur with higher doses and sometimes even with chronic administration of low doses. Therefore, these agents are most effective when given in combination with a thiazide to maintain antihypertensive efficacy and minimize potential edema.

Aliskiren

Aliskiren is the only direct renin inhibitor. This drug blocks the RAAS at its point of activation, which results in reduced plasma renin activity and BP lowering.

The role of this drug class in the management of hypertension is limited. Since aliskiren is a RAAS blocker, it should not be used in combination with an ACEi or an ARB because of a higher risk of serious adverse effects without providing any additional reduction in CV events.[1]

Many of the cautions and adverse effects observed with an ACEi or ARB apply to aliskiren. Aliskiren should never be used in pregnancy due to the known teratogenic effects of using other drugs that block the RAAS system. Angioedema has also been reported in patients treated with aliskiren, as well as increases in serum creatinine and serum potassium values. The mechanisms of these adverse effects are likely similar to those with an ACEi or ARB. It is reasonable to utilize similar monitoring strategies by measuring serum creatinine and serum potassium in patients treated with aliskiren.

Central α_2-Agonist

Clonidine, 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, CO, TPR, plasma renin activity, and baroreceptor reflexes. Clonidine is usually reserved for resistant hypertension, and methyldopa, when used, is primarily for pregnancy-induced hypertension.

Chronic use of centrally acting α_2-agonist results in sodium and water retention, which is most prominent with methyldopa. Low doses of clonidine and guanfacine can be used to treat hypertension without the addition of a thiazide. However, methyldopa should be given in combination with a thiazide to avoid blunting the antihypertensive effect that happens with prolonged use when treating chronic hypertension (but not in pregnancy). Sedation and dry mouth are common anticholinergic side effects that typically improve with chronic use of low doses, but they are more troublesome in older patients. As with other centrally acting antihypertensives, depression can occur, especially with high doses. The incidence of orthostatic hypotension and dizziness is higher than with other antihypertensive agents, so they should be used 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 older patients.

Abrupt cessation of a central α_2-agonist 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 discontinued, it should be tapered. For patients who are receiving concomitant β-blocker therapy, the β-blocker should be gradually discontinued first several days before gradual discontinuation of clonidine. Considering the increased risk of adverse effects and the need for frequent administration with the oral dosage formulation, which increases the risk of rebound hypertension during periods of nonadherence, the transdermal form rather than tablets should be used when clonidine therapy is needed.[69]

Methyldopa can cause hepatitis or hemolytic anemia, although this is rare. Methyldopa should be quickly discontinued if persistent increases in serum hepatic transaminases or alkaline phosphatase are detected because this may indicate the onset of fulminant life-threatening hepatitis. Coombs-positive hemolytic anemia occurs in <1% of patients receiving methyldopa, although 20% exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited use in the routine management of hypertension, except in pregnancy.

Direct Arterial Vasodilator

Hydralazine and minoxidil directly relax arteriolar smooth muscle resulting in vasodilation and BP lowering. They exert little to no venous vasodilation.

Both agents cause potent reductions in perfusion pressure that activate baroreceptor reflexes. Activation of baroreceptors results in a compensatory increase in sympathetic outflow, which leads to an increase in heart rate, CO, and renin release. Consequently, tachyphylaxis (loss of antihypertensive effect) can develop with continued use. This compensatory baroreceptor response can be counteracted by concurrent use of a β-blocker.

All patients receiving hydralazine or minoxidil for chronic therapy should first receive both a thiazide and a β-blocker. Direct arterial vasodilators can precipitate angina in patients with stable ischemic heart disease unless the baroreceptor reflex mechanism is blocked with a β-blocker (diltiazem or verapamil can be used as an alternative to β-blockers for this purpose). The side effect of sodium and water retention is significant but is minimized by using a thiazide concomitantly.

One side effect unique to hydralazine is a dose-dependent drug-induced lupus-like syndrome. Hepatic *N*-acetyltransferase eliminates hydralazine. 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 on discontinuation. Drug-induced lupus may be avoided by using less than 200 mg of hydralazine daily. Because of side effects, hydralazine has limited clinical use for chronic management of hypertension. However, it is especially useful for patients with severe CKD and kidney failure. When used in combination with isosorbide dinitrate, hydralazine has been shown to reduce the risk of CV events in Black patients with HFrEF when added to a standard regimen of a diuretic, ACEi, or ARB, and evidence-based β-blocker therapy.[44]

Minoxidil is a more potent vasodilator than hydralazine. Therefore, the compensatory increases in heart rate, CO, renin release, and sodium retention are even more dramatic. Due to significant water retention, 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. Hypertrichosis usually ceases when the drug is discontinued. Other minoxidil side effects include pericardial effusion and a nonspecific T-wave change on the electrocardiogram. Minoxidil is reserved for resistant hypertension as an alternative to hydralazine.

Combination Therapy

13 A combination of two antihypertensive drugs is recommended for patients initially presenting with stage 2 hypertension.[1] Using a fixed-dose combination product is an option for these types of patients and has been shown to improve adherence. Initial two-drug combination therapy may also be appropriate for patients with multiple compelling indications for different antihypertensive agents. Moreover, combination therapy is often needed to control BP in patients who are already treated with drug therapy.[1]

The long-term safety and efficacy of initial two-drug therapy for hypertension were evaluated in the ACCOMPLISH trial.[83] This was a prospective, randomized, double-blind trial in 11,506 patients with hypertension and other CV risk factors. All these patients either had stage 2 hypertension or were on antihypertensive drug therapy at enrollment. Patients were randomized to receive either benazepril-with-hydrochlorothiazide or benazepril-with-amlodipine as initial drug therapy. Treatment was titrated to a goal BP of <140/90 mm Hg for most patients and <130/80 mm Hg for patients with diabetes or CKD.

The trial was terminated early after a mean of 36 months because the incidence of CV events was 20% lower in the benazepril-with-amlodipine group compared with the benazepril-with-hydrochlorothiazide group. What is most important for clinical practice is that this trial established that initial two-drug therapy for stage 2 hypertension was safe and effective. Mean BP measurements were 132/73 and 133/74 mm Hg in the benazepril-with-amlodipine and benazepril-with-hydrochlorothiazide groups.

The ACCOMPLISH trial established initial two-drug antihypertensive therapy as an evidence-based strategy to treat hypertension. Clinicians should consider this study as justification for implementing initial two-drug therapy antihypertensive regimens in appropriate patients. Moreover, the ACCOMPLISH trial demonstrated that the combination of an ACEi with a dihydropyridine CCB was more effective in reducing CV events than the combination of an ACEi with hydrochlorothiazide. However, thiazides are effective at lowering BP, particularly chlorthalidone and indapamide, especially when combined with other agents, and hydrochlorothiazide is available in many fixed-dose combination products.

Optimal Use of Combination Therapy

Clinicians should anticipate the need for combination therapy to control BP in most patients. Using low-dose combinations also provides greater BP reductions than high doses of single agents, with fewer drug-related side effects.[71] Contrary to popular myth, appropriately increasing the number of antihypertensive medications to attain goal BP values does not increase the risk of adverse effects. The American Society of Hypertension has

recommended three categories of combination therapy (see **Box B**).[84] Preferred combinations are ideal for lowering BP, have complementary mechanisms of action, and use evidence-based first-line agents. Acceptable combinations may not provide all of the benefits that preferred combinations do and may have additive side effect profiles. Less-effective combinations are limited in their overall benefits and should only be used when necessary, except when treating compelling indications.

Box B

American Society of Hypertension Recommendations for Combination Therapy

Preferred	Acceptable	Less Effective
• ACEi/CCB	• β-Blocker/thiazide	• ACEi/β -blocker
• ARB/CCB	• CCB (dihydropyridine)/β -blocker	• ARB/β -blocker
• ACEi/thiazide	• CCB/thiazide	• CCB (nondihydropyridine)/β -blocker
• ARB/thiazide	• Thiazide/potassium-sparing diuretic	• Centrally acting agent/β -blocker

Data from Reference 85.

Some combinations should be avoided when treating hypertension. As previously discussed, the ON-TARGET demonstrated that using an ACEi with an ARB in the management of hypertension resulted in no additional reduction in the incidence of CV events.[85] Moreover, this combination resulted in a higher risk of adverse events, which was also demonstrated in other trials. These same negative effects are seen when aliskiren is used in combination with an ARB.[86] These combinations (using two RAAS blockers together) should be avoided in the management of hypertension.[1] Other combinations, such as a thiazide with a potassium-sparing diuretic, both of which have overlapping mechanisms of action, should be implemented only to minimize hypokalemia; not for additional BP lowering. Combining two CCBs, a dihydropyridine with a nondihydropyridine, can provide additional BP lowering but has limited use in the routine management of most patients. Under no circumstance should two drugs from the exactly same class of medications be used to treat hypertension.

Fixed-Dose Combination Products

Many fixed-dose combination products are available, and nearly all are generic (see Table 30-9). Most combination products contain a thiazide and have multiple dose strengths. Individual dose titration is more complicated with fixed-dose combination products, but this strategy can reduce the number of daily tablets/capsules and simplify regimens to improve adherence by decreasing pill burden. This alone may increase the likelihood of achieving or maintaining goal BP values and is recommended to improve adherence.[1,87] Most generic combination products are less expensive to patients and health systems. Nonadherence rates are lower when fixed-dose combination products are used to treat hypertension compared with using free drug components (separate pills) to treat hypertension and therefore is recommended preferentially.[1]

TABLE 30-9

Fixed-Dose Combination Products

Combination	Medication (Brand Name)
ACEi with CCB	• Amlodipine/benazepril (Lotrel) • Perindopril/amlodipine (Prestalia) • Trandolapril/verapamil (Tarka)
ARB with CCB	• Amlodipine/olmesartan (Azor) • Telmisartan/amlodipine (Twynsta) • Valsartan/amlodipine (Exforge)
ACEi with a thiazide	• Benazepril/hydrochlorothiazide (Lotensin HCT) • Captopril/hydrochlorothiazide (Capozide) • Enalapril/hydrochlorothiazide (Vaseretic) • Fosinopril/hydrochlorothiazide (Monopril HCT) • Lisinopril/hydrochlorothiazide (Prinizide, Zestoretic) • Moexipril/hydrochlorothiazide (Uniretic) • Quinapril/hydrochlorothiazide (Accuretic)
ARB with a thiazide	• Azilsartan/chlorthalidone (Edarbyclor) • Candesartan/hydrochlorothiazide (Atacand HCT) • Eprosartan/hydrochlorothiazide (Teveten HCT) • Irbesartan/hydrochlorothiazide (Avalide) • Losartan/hydrochlorothiazide (Hyzaar) • Olmesartan/hydrochlorothiazide (Benicar HCT) • Telmisartan/hydrochlorothiazide (Micardis HCT) • Valsartan/hydrochlorothiazide (Diovan HCT)
β-Blocker with a thiazide	• Atenolol/chlorthalidone (Tenoretic) • Bisoprolol/hydrochlorothiazide (Ziac) • Metoprolol succinate/hydrochlorothiazide (Dutoprol) • Metoprolol tartrate/hydrochlorothiazide (Lopressor HCT) • Nadolol/Bendroflumethiazide (Corzide) • Propranolol/hydrochlorothiazide (Inderide)
Direct renin inhibitor with thiazide	Aliskiren/hydrochlorothiazide (Tekturna HCT)
Mineralocorticoid receptor antagonist with thiazide	Spironolactone/hydrochlorothiazide (Aldactazide)
ARB with CCB with a thiazide	• Amlodipine/valsartan/hydrochlorothiazide (Exforge HCT) • Olmesartan/amlodipine/hydrochlorothiazide (Tribenzor)

Chronotherapy

Chronotherapy refers to targeting medication release and its effects at specific times of the day. The rationale behind chronotherapy in hypertension is that blunting the early morning BP surge may result in more significant reductions in CV events than dosing conventional antihypertensive products in the morning.

Two nondihydropyridine CCBs, sustained-release verapamil (Verelan PM) and long-acting diltiazem (Cardizem LA), are designed to target the circadian BP rhythm. When dosed in the evening, the drug is released during the early morning hours when BP first increases. However, evidence from the Controlled Onset Verapamil Investigation of Cardiovascular End-Points (CONVINCE) trial showed that chronotherapeutic verapamil was similar to, but not better than, a thiazide–β-blocker–based regimen for CV events.[27]

The Hygia Chronotherapy Trial sought to assess whether dosing one or more antihypertensives at bedtime reduced CVD events more than upon waking.[88] The trial reported that evening dosing dramatically reduced CV events and CV death. However, results of the Hygia trial should be viewed cautiously due to several issues, including the methods (eg, open-label design, statistics used), and the magnitude of benefit on CV outcomes was inconsistent with the minimal BP difference between groups (1 mm Hg). Therefore, data are lacking based on the current evidence, demonstrating an advantage for chronotherapy in treating hypertension.

Pharmacoeconomic Considerations

The cost of effectively treating hypertension based on estimated annual healthcare expenditures is approximately $2,000 more for patients with hypertension than without hypertension.[89] The average yearly direct and indirect cost of hypertension from 2016 to 2017 was $52.4 billion.[90,91] However, costs of care are offset by savings that would be realized by reducing CV morbidity and mortality. Costs related to treating CV events (eg, MI, end-stage kidney failure) can drastically increase healthcare costs.

Antihypertensive drug costs are generally inexpensive and are not a significant portion of the total cost of hypertensive care. Nearly all antihypertensive agents, including first-line antihypertensive drug classes (ACEis, ARBs, CCBs, and thiazides), are generic. Many are available on discount formularies, including many generic fixed-dose combinations.

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. An ACEi, ARB, CCB, and thiazide are all first-line treatment options in most patients without compelling indications, and with few exceptions, are inexpensive. Utilizing generic agents, either as monotherapy or combined, is appropriate under nearly all circumstances in hypertension management. Use of once-daily and fixed-dose generic combination antihypertensives that are economical is preferred.[1]

Team-Based Collaborative Care

Team-based care for patients with cardiovascular disease is optimal for the comprehensive care of patients.[1] A collaborative approach to the management of hypertension is a proven strategy that improves goal BP attainment rates.[1] Ideal patient care models are interprofessional and utilize physicians, pharmacists, nurses, and other healthcare professionals.

With the advent of healthcare reform, collaborative team-based approaches to chronic diseases are viewed as high-quality and cost-effective improvement modalities. Within these models, pharmacists have been proven to be an effective component of team-based models not only in a community pharmacy or ambulatory clinic settings[92] but also in community outreach sites such as barbershops.[93] In addition to optimizing the selection and implementation of antihypertensive drug therapy and increased attainment of goal BP, clinical interventions by pharmacists have been proven to reduce the risk of adverse drug events and medication errors in ambulatory patients with CV disease.[94] Pharmacists have a substantial effect in various roles in clinical settings, through comprehensive medication management, optimization of drug use, avoidance of adverse drug events, and patient education.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring the Pharmacotherapy Plan

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

Efficacy

The most important strategy to prevent CV morbidity and mortality from CV events in hypertension is BP control to a goal (see Box A). Treating to a goal BP of <130/80 mm Hg should be attained in older patients and those with isolated systolic hypertension. For older patients, actual BP lowering can occur at a more gradual pace to avoid orthostatic hypotension. Modifying other CV risk factors (eg, smoking, dyslipidemia, diabetes) is also essential.

Both clinic-based and self-measurement home BP monitoring are important components for monitoring and managing hypertension. Patients should be encouraged to obtain a validated home BP monitor, record the results, and send or bring them to follow-up clinic visits. BP response should be evaluated in the clinic 4 weeks after initiating or making changes in therapy and results compared to home BP readings. Once goal BP is attained, clinic BP monitoring can be done every 3 to 6 months. More frequent evaluations are required for patients with a history of poor control, nonadherence, other significant comorbidities, or symptoms of adverse drug effects.

Automated ABP monitoring can be useful clinically to establish effective 24-hour control. This type of monitoring may become the standard of care in the future because evolving data have demonstrated significant benefits of using these types of measurements to diagnose hypertension, confirm white coat or masked uncontrolled hypertension, and could be a stronger predictor of CVD.[1]

For patients self-measuring their BP at home, it is important that they measure during the early morning hours, taking at least two measurements 1 minute apart before taking antihypertensive medications, for most days and then in the evening on alternate days of the week using appropriate technique.[1] BP measurements should be recorded daily, or ideally, a monitor with a built-in memory should be used. Patients should be instructed to bring their actual measurements and/or BP monitor with built-in memory to follow-up clinic appointments, and any changes to drug therapy should be based on an average BP reading from two or more occasions.[1]

Side Effects and Toxicity

The most common side effects associated with each class of antihypertensive agents were discussed in the "First-Line Antihypertensive Agents" and "Alternative Agents" sections, and laboratory parameters for first-line agents are listed in Table 30-10. Laboratory monitoring should typically occur 4 weeks after starting a new agent or dose increase, and then every 6 to 12 months in stable patients. Additional disease-specific monitoring might be needed (eg, diabetes, dyslipidemia, gout) depending on which agents are used. Moreover, patients treated with a mineralocorticoid receptor antagonist (eplerenone or spironolactone) should ideally have potassium concentrations and kidney function assessed within 3 days of initiation and again at 1 week to detect potential hyperkalemia, especially for patients at high risk for hyperkalemia. The occurrence of an adverse drug event may require dosage reduction or substitution with an alternative antihypertensive agent.

TABLE 30-10

Routine Monitoring for Select Antihypertensive Agents

Class	Parameters
ACEi	BP; BUN/serum creatinine; serum potassium
ARB	BP; BUN/serum creatinine; serum potassium
β-Blocker	BP; heart rate
Calcium channel blocker	BP; heart rate
Mineralocorticoid receptor antagonist	BP; BUN/serum creatinine; serum potassium
Thiazide	BP; BUN/serum creatinine; serum electrolytes (potassium, magnesium, sodium); uric acid (for thiazides)

Disease Progression

Patients should be monitored for signs and symptoms of hypertension-associated complications. A careful history for ischemic 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 determine the presence of CV and cerebrovascular disease. Other monitoring parameters that may be used include funduscopic changes on an eye examination, LVH on electrocardiogram, albuminuria, and changes in kidney function by calculating estimated GFR. These parameters should be monitored periodically because any sign of deterioration requires additional assessment and follow-up.

Adherence and Persistence

Poor medication use behaviors and lack of persistence with antihypertensive pharmacotherapy is a major problem and associated with significant increases in costs due to the development of complications. Since hypertension is nearly always an asymptomatic disease, poor adherence is frequent, particularly in newly treated patients. Up to 25% of patients do not fill their initial prescription for antihypertensive medication, and during the first year of treatment, an average patient possesses their BP medication only half of the time.[1] Long-term risk of CV events can be significantly reduced when patients adhere to their antihypertensive drug therapy. Therefore, it is imperative to assess patient adherence and medication-taking behavior on a regular basis.

Improving adherence to antihypertensive treatment and hypertension control requires a multifactorial approach.[1] These include interventions aimed at the patient, provider, and health-system level. Examples can include (a) focusing on clinical outcomes (eg, following national guidelines, use of once-daily antihypertensives and combination rather than free individual components, encouraging self-monitoring of BP), (b) empowering informed activated patients (eg, behavioral and motivational strategies, use of pillboxes, systems to prompt patients to refill prescriptions), (c) implementing a team approach (eg, collaborative interprofessional models of care), (d) use of telehealth strategies, and (e) advocating for health policy reform (eg, use of performance measures, reimbursement for telehealth strategies).

After identifying less than optimal adherence in a patient with hypertension, appropriate patient education, counseling, and intervention should occur. Once-daily regimens are recommended in most patients to improve adherence. Some patients may incorrectly believe that aggressive treatment may negatively impact the quality of life and thus result in nonadherence. However, several studies have found that most patients feel better once their BP is controlled, and patients should be aware of this. Patients on antihypertensive therapy should be questioned periodically about changes in their general health perception, physical functioning, and overall satisfaction with treatment. Lifestyle modifications should always be recommended to augment antihypertensive drug therapy and provide other potential health benefits. Persistence with lifestyle modifications should also be continually encouraged.

Hypertensive Urgencies and Emergencies

Both hypertensive urgencies and emergencies (aka hypertensive crisis) are characterized by elevated BP, typically >180/120 mm Hg.[1] However, the need for urgent or emergent antihypertensive therapy must be determined based on the presence of acute or immediately progressing end-organ injury, not elevated BP alone. Urgencies are not associated with acute or immediately progressing end-organ injury, while emergencies are. Examples of acute end-organ injury include encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, acute renal failure, and eclampsia.

Hypertensive urgencies are ideally managed by adjusting maintenance therapy, whereas hypertensive emergencies require immediate BP reduction parenteral agents to limit new or progressing end-organ damage. The Acute Hypertensive Crisis Chapter (Chapter e31) discusses the pathophysiology and pharmacotherapeutic treatment of hypertensive urgencies and emergencies.

CONCLUSIONS

Hypertension is a common medical condition in the United States with significant health consequences if not controlled. Treatment of patients with hypertension should include both lifestyle modifications and pharmacotherapy. Evidence from outcome-based clinical trials has 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. An ACEi, ARB, CCB, and thiazide are all first-line agents. Data suggest that using a β-blocker first-line to treat patients with hypertension, without the presence of a compelling indication, is better than not treating hypertension. However, β-blocker therapy is not as beneficial in reducing the risk of CV events compared with ACEi-, ARB-, CCB-, or thiazide-based therapy and is not a first-line therapy option without an appropriate compelling indication.

Patients should be treated to a goal BP value. In addition to selecting an appropriate antihypertensive regimen, attaining a goal BP is also of paramount importance to ensure a maximum reduction in risk for CV events is provided. A BP goal of <130/80 mm Hg is recommended for most patients with hypertension. Most patients with hypertension require more than one drug to attain goal BP values; therefore, combination therapy should be anticipated.

Optimizing hypertension management can be achieved in many ways. Team-based approaches to implementing care and attaining goal BP values are preferred. Judicious use of cost-effective medications and fixed-dose combination products should always be considered to improve the sustainability of treatment. Lastly, interventions to reinforce adherence and lifestyle modifications are needed for the comprehensive management of hypertension.

ABBREVIATIONS

ABP	ambulatory blood pressure
ACC	American College of Cardiology
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension
ACCORD-BP	Action to Control Cardiovascular Risk in Diabetes Blood Pressure
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease

AT_1	angiotensin II type 1
AT_2	angiotensin II type 2
BP	blood pressure
BUN	blood urea nitrogen
CCB	calcium channel blocker
CKD	chronic kidney disease
CO	cardiac output
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular End-Points
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
GEMINI	Glycemic Effects in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives
GFR	glomerular filtration rate
HOT	Hypertension Optimal Treatment
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HYVET	Hypertension in the Very Elderly Trial
INVEST	International Verapamil–Trandolapril Study
ISA	intrinsic sympathomimetic activity
KDIGO	Kidney Disease Improving Global Outcomes
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MI	myocardial infarction
MOSES	Morbidity and Mortality After Stroke: Eprosartan Versus Nitrendipine in Secondary Prevention

MRA	mineralocorticoid receptor antagonists
MRC	Medical Research Council
NHLBI	National Heart, Lung, and Blood Institute
ON-TARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial
PAD	peripheral arterial disease
PATHWAY-2	Prevention And Treatment of Hypertension With Algorithm based therapY-2
PVR	peripheral vascular resistance
RAAS	renin–angiotensin–aldosterone system
SBP	systolic blood pressure
SHEP	Systolic Hypertension in the Elderly Program
SPRINT	Systolic Pressure Intervention Trial
STOP-2	Swedish Trial in Old Patients with Hypertension-2
STOP-Hypertension	Swedish Trial in Old Patients with Hypertension
Syst-Eur	Systolic Hypertension in Europe
TOMHS	Treatment of Mild Hypertension Study
TPR	total peripheral resistance
TRANSCEND	Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease
UKPDS	United Kingdom Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation

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SELF-ASSESSMENT QUESTIONS

Use the following scenario for the next two questions: A 78-year-old Hispanic man has a past medical history of hypertension for 10 years. His BP today is 158/82 mm Hg (156/84 mm Hg when repeated), heart rate is 70 beats/min, serum creatinine is 1.2 mg/dL (106 µmol/L) (eGFR 58 mL/min/1.73m^2), and potassium is 4.3 mEq/L (mmol/L). He is adherent with benazepril 40 mg daily and amlodipine 10 mg daily, weighs 93 kg, is 67″ (170 cm) tall (BMI 32 kg/m^2), smokes one-half pack cigarettes daily, and consumes two to three ethanol-containing drinks weekly.

1. Which of the following is the most appropriate medication to add to his antihypertensive regimen?

   A. Verapamil

   B. Irbesartan

   C. Chlorthalidone

   D. Metoprolol succinate

2. Which of the following lifestyle changes would most likely produce the greatest decrease in BP?

   A. Weight loss of 5 kg

   B. Smoking cessation

   C. Decrease dietary sodium by 500 mg/day

   D. Decreasing ethanol consumption by 50%

Use the following scenario for the next three questions: A 40-year-old black woman has a BP measurement of 150/110 mm Hg when she first arrives for a routine physical examination by a medical assistant. She has no previous history of hypertension. She is extensively interviewed and examined, and has no signs of acute or chronic hypertension-associated end-organ damage. Her physician measures her BP again 20 minutes later, and it is 142/98 mm Hg (140/100 mm Hg when repeated). Her most recent fasting lipid panel was also normal, and her 10-year ASCVD risk score is 1.2%. She is instructed to measure her BP at home twice each morning. After 2 weeks, her average home BP is 138/96 mm Hg.

3. Which of the following is the most accurate clinical assessment of her present situation?

   A. White coat hypertension

   B. Elevated blood pressure

   C. Stage 1 hypertension

   D. Stage 2 hypertension

4. Which of the following is the most appropriate BP goal in this patient?

   A. <120/80 mm Hg

   B. <130/80 mm Hg

   C. <140/90 mm Hg

   D. <150/90 mm Hg

5. Which of the following is the most appropriate plan for this patient now?

   A. Lifestyle modifications, continue home BP monitoring and re-evaluate in 3 months

   B. Lifestyle modifications, continue home BP monitoring, start lisinopril, and re-evaluate in 1 month

   C. Lifestyle modifications, continue home BP monitoring, start hydrochlorothiazide, and re-evaluate in 1 month

   D. Lifestyle modifications, continue home BP monitoring, start lisinopril and amlodipine, and re-evaluate in 1 month

6. A 60-year-old woman with hypertension, type 2 diabetes, and HFrEF is seen 2 months after experiencing an acute myocardial infarction. Her present BP is 110/74 mm Hg (112/76 mm Hg when repeated) and her heart rate is 60 beats/min. Her serum creatinine is 1.1 mg/dL (97 µmol/L), serum

potassium is 3.5 mEq/L (mmol/L), and spot urinalysis shows 20 mg albumin/g (2.26 mg/mmol) creatinine. She currently has no peripheral or pulmonary edema. She is taking furosemide 40 mg twice daily, carvedilol 25 mg twice daily, and enalapril 20 mg twice daily. Which of the following statements is most appropriate to include when counseling this patient regarding her antihypertensive therapy?

A. It is possible to stop enalapril because BP is at goal.

B. Long-term benefits of carvedilol and enalapril are a reduced risk of CV events.

C. If you experience new onset depression, you should stop taking carvedilol.

D. If you experience dry cough, stop taking enalapril immediately because this can lead to angioedema.

7. Which of the following statements is true regarding ARBs in the treatment of hypertension?

A. An ARB is first-line for most patients because of demonstrated BP lowering and reduced risk of CV events.

B. The ALLHAT study showed that nonfatal MI and coronary heart disease are reduced equally with ARB therapy compared with amlodipine or chlorthalidone.

C. An ARB is preferred over an ACEi in patients with chronic kidney disease who have albuminuria.

D. An ACEi should only be added to ARB therapy in patients who are not at their BP goal value despite titrating to maximum ACEi dose.

8. Which of the following is true regarding patients with elevated BP of 120-129 mm Hg and a diastolic BP <80 mm Hg according to the 2017 ACC/AHA guideline?

A. These patients are classified as elevated BP.

B. Lifestyle modifications should be recommended with re-evaluation in 12 months.

C. Approximately 50% of these patients with elevated BP eventually develop hypertension within their lifetime.

D. These patients have equal CV risk compared to patients with normal BP values.

Use the following case for the next two questions: A 70-year-old White woman with hypertension and type 2 diabetes has been on diltiazem extended-release 360 mg daily for 6 years. She was on lisinopril several years ago, but it was stopped due to angioedema. She was first diagnosed with hypertension when her BP was 180/82 mm Hg. Today, her BP is 148/78 mm Hg (146/76 mm Hg when repeated) and her heart rate is 100 beats/min. Her urinalysis shows a spot urine albumin/creatine ratio of 100 mg/g (11.3 mg/mmol), serum creatinine is 1.6 mg/dL (141 µmol/L)(eGFR 37 mL/min/1.73m^2), potassium is 4.1 mEq/L (mmol/L), weight is 75 kg, and height is 66 inches (168 cm). These are similar to values measured 3 months ago. Her only complaint is headache.

9. Which of the following is/are routine monitoring parameters/tests that is needed because of her current antihypertensive drug therapy?

A. Heart rate

B. Serum potassium, sodium, and magnesium

C. Serum creatinine and BUN

D. Electrocardiogram

10. Olmesartan 20 mg daily is added to her regimen. Four weeks later, her BP is 136/72 and 138/74 mm Hg, serum creatinine is 1.8 mg/dL (159 µmol/L), and potassium is 4.5 mEq/L (mmol/L). Which of the following is the most appropriate option to treat this patient's hypertension?

A. Increase olmesartan to 40 mg daily.

B. Add hydrochlorothiazide 25 mg daily.

C. Add spironolactone 25 mg daily.

D. Replace olmesartan with carvedilol 12.5 mg twice daily.

11. Which of the following is true regarding the use of arterial vasodilators (hydralazine or minoxidil) in the treatment of hypertension?

A. Severe bradycardia occurs when they are used in combination with a β-blocker.

B. Both can cause severe rebound hypertension when stopped abruptly.

C. Both are poorly tolerated because of anticholinergic side effects.

D. Both should be given in combination with a diuretic and a β-blocker.

12. A 65-year-old woman with type 2 diabetes, hypertension, osteoporosis, and atrial fibrillation has a BP of 150/96 mm Hg (150/90 mm Hg when repeated), heart rate of 68 beats/min, potassium of 3.3 mEq/L (mmol/L), and a serum creatinine of 2.3 mg/dL (203 μmol/L). She reports an "allergy" to hydrochlorothiazide (severe gout). Presently, she is on verapamil CD 480 mg daily. Which of the following drug regimens would be the most appropriate to add to her regimen?

A. Chlorthalidone 12.5 mg daily

B. Amlodipine 5 mg daily

C. Atenolol 25 mg daily

D. Valsartan 160 mg daily

13. Which of the following is preferred as add-on therapy for a patient who is post-MI (3 months ago) with a BP of 136/88 mm Hg (134/86 mm Hg when repeated) while treated with metoprolol succinate 200 mg daily?

A. Chlorthalidone

B. Verapamil

C. Amlodipine

D. Lisinopril

14. Which of the following is preferred as initial antihypertensive therapy for a 63-year-old woman who is diagnosed with hypertension and has a history of ischemic stroke (6 months ago), with a BP of 186/108 mm Hg (184/106 mm Hg when repeated)?

A. A thiazide with an ACEi

B. A thiazide with a nonselective β-blocker

C. A thiazide alone

D. An ACEi with an ARB

15. A 52-year-old man has a history of asthma, chronic stable angina, and hypertension. He is experiencing ischemic chest pain twice weekly while being treated with bisoprolol 10 mg daily. His BP is 146/90 mm Hg (144/92 mm Hg when repeated), and heart rate is 58 beats/min. Which of the following would be most appropriate to add to this patient's regimen?

A. Lisinopril 20 mg daily

B. Diltiazem SR 180 mg daily

C. Amlodipine 5 mg daily

D. Irbesartan 150 mg daily and hydrochlorothiazide 25 mg daily

Use the following case for the next three questions: A 69-year-old Black woman with a history of angioedema (from lisinopril), hypertension, and type 2 diabetes is currently receiving hydrochlorothiazide 25 mg daily and carvedilol 25 mg twice daily. Today her BP is 138/82 mm Hg (138/84 mm Hg when repeated) and heart rate is 50 beats/min. Urinalysis shows a spot urine/creatine ratio 400 mg/g (45.2 mg/mmol), serum creatinine is 1.2 mg/dL (106 µmol/L) (eGFR 57 mL/min/1.73m^2), potassium is 3.8 mEq/L (mmol/L), weight is 90 kg, and height is 65 inches (165 cm). She complains of heartburn, a dry cough, constipation, and severe fatigue especially when she tries to exercise. She normally exercises three times per week, but has not been able to since her last medical visit, and follows a DASH eating plan.

16. Which of her complaints is most likely from one of her antihypertensive medications?

A. Heartburn

B. Dry cough

C. Constipation

D. Fatigue

17. Which of the following is the most appropriate modification to her regimen?

A. Decrease carvedilol to 12.5 mg twice daily and add lisinopril.

B. Decrease carvedilol to 12.5 mg twice daily and add irbesartan.

C. Stop hydrochlorothiazide and start spironolactone and felodipine.

D. Stop carvedilol and start valsartan.

18. The patient reports taking several nonprescription medications including aspirin 81 mg daily, a multivitamin daily, acetaminophen, and loratadine. She asks you if these are safe to take because of her hypertension. Which of the following is the most appropriate response?

A. You should stop taking these until you have discussed this with your primary care physician.

B. Acetaminophen can increase your blood pressure; you should use naproxen instead.

C. Loratadine can increase your blood pressure; you should use pseudoephedrine if needed.

D. These medications are generally safe to use in patients with hypertension, even if not controlled.

19. A 55-year-old man with hypertension and no other chronic medical problems is currently treated with hydrochlorothiazide 50 mg daily, irbesartan 300 mg daily, carvedilol 25 mg twice daily, and amlodipine 10 mg daily. His BP is 144/96 mm Hg (146/94 mm Hg when repeated). He is adherent with all of these medications and with lifestyle modifications. Serum creatinine is 1.2 mg/dL (106 µmol/L), potassium is 3.7 mEq/L (mmol/L), and all other laboratory values are normal. Which of the following is the most appropriate to add to his regimen?

A. Terazosin 2 mg daily

B. Spironolactone 25 mg daily

C. Clonidine 0.1 mg twice daily

D. Chlorthalidone 25 mg daily

20. A 40-year-old man with newly diagnosed hypertension asks you for advice regarding lifestyle modifications to lower BP. He has no other past medical history, is 72 inches (183 cm) tall, weighs 120 kg, and does not follow any particular diet. He eats red meat most days of the week, eats lunch

out at work Monday through Friday, eats breakfast and dinner at home most days, and drinks 1 beer/week. He does not exercise. Which of the following is an appropriate recommendation?

A. Lose weight

B. Increase your daily ingestion of potassium and sodium

C. Start 60 minutes of vigorous exercise most days of the week

D. Decrease your daily fiber intake

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The patient has uncontrolled hypertension. Although he is older, he does not have a limited life expectancy, is not living in a nursing home, a goal of <130/80 mm Hg is appropriate. He is already on two first-line agents with an ACEi and a dihydropyridine CCB. The most appropriate addition to his current therapy would be a thiazide diuretic (see Fig. 30-2). A thiazide-type diuretic is a first-line agent for this patient who has no other compelling indications for specific antihypertensive drug therapy, and should be effective in lowering BP as an addition to his current regimen. Although verapamil is a non-dihydropyridine CCB adding it to amlodipine, which is a non-dihydropyridine CCB, not be a complimentary combination regimen. Adding irbesartan would be harmful because it is an ARB and she is already on an ACEi (benazepril) and this type of combination can increase risk of adverse effects and should be avoided.

2. **A.** Weight loss is the most likely to result in the greatest BP lowering, particularly considering the patient is obese (his BMI is ≥ 30 kg/m^2). The extent that BP is lowered with weight loss is directly associated to the amount of weight loss achieved. Smoking increases the risk of ASCVD, and smoking cessation should be recommended to reduce overall risk of ASCVD. Smoking does not increase BP chronically and it is not a secondary cause of hypertension, so smoking cessation is not a modality to lower BP. Likewise, the magnitude of sodium reduction listed (only 500 mg/day) is fairly low and is not expected to significantly lower BP. The patient's current alcohol consumption is under the current recommended maximum intake, so further restriction is not necessary. See Table 30-4.

3. **D.** This patient has several BP measurements from multiple clinical visits that are ≥130/80 mm Hg, so she meet the criteria for the diagnosis of hypertension. Because the patient's SBP is ≥140 mm Hg and diastolic is ≥90 mm Hg, she is categorized as stage 2 hypertension. She does not have white coat hypertension because her average out-of-office (home) BP measurement (138/96 mm Hg) is similar to the last BP measurements of 142/98 and 140/100 mm Hg. If her average home BP value was 130-139/80-89 mm Hg, she would be considered to have stage 1 hypertension, and if 120-129/<80 mm Hg, it would be categorized as elevated. See Table 30-3.

4. **B.** The goal BP per the 2017 ACC/AHA High Blood Pressure Guideline is <130/80 mm Hg. The option of <120/80 mm Hg is considered a normal BP, but is never a goal of therapy. The options of <140/90 or <150/90 mm Hg are no longer recommended by the 2017 ACC/AHA High Blood Pressure Guideline.

5. **D.** Lifestyle modification is always recommended for any patient, especially when BP is ≥120/80 mm Hg. Continuing home BP monitoring is reasonable because she is already doing it and home BP monitoring is a modality to engage patients with their disease and it's use is associated with a higher rate of achieving goal BP. This patient has stage 2 hypertension with diastolic BP >10 mm Hg from goal. Therefore, combination therapy with two first-line antihypertensives, in addition to lifestyle modifications, is recommended, with re-evaluation in 1 month. This would also be recommended if her systolic BP was >20 mm Hg from goal. Lifestyle modifications alone with re-evaluation in 3 months would be appropriate if she were in stage 1 hypertension because her 10-year ASCVD risk is <10%, and if continually in stage 1 after 3 to 6 months monotherapy with hydrochlorothiazide (preferred because she is a Black woman) would be reasonable. Under that circumstance, monotherapy with lisinopril (an ACEi) would be less desirable because she is African American and at age 40 may be of childbearing potential and would need to be on a reliable form of contraception if sexually active due to the potential harm of using an ACEi if she were to become pregnant. See Fig. 30-2 and Box B.

6. **B.** With a history of an acute MI as well as HFrEF, the patient has compelling indications for both an ACEi and β-blocker. These medications reduce the risk of CV events in HFrEF and in patients with stable ischemic heart disease (history of myocardial infarction). Specifically, in HFrEF carvedilol, metoprolol succinate or bisoprolol are considered proven β-blocker in HFrEF, and use of most β-blockers post-myocardial infarction is proven to reduce mortality and risk of recurrent myocardial infarction. Stopping enalapril is not reasonable considering her high ASCVD risk, even if at BP

goal. Counseling patients to stop a β-blocker if they experience depression would be harmful and would induce rebound hypertension if not slowly tapered. Although cough is a risk of ACEi therapy, which is annoying, it does not lead to angioedema. See section Key Concept 10. Patients with Compelling Indications.

7. **A.** An ARB is considered a first-line agent for the treatment of hypertension. ARBs were not studied in ALLHAT, are not preferred over an ACEi in patients with CKD who have albuminuria, and should not be used in combination with an ACEi. See the "First-Line Antihypertensive Agents" section.

8. **A.** A patient with a BP of 120-129/<80 mm Hg would be considered to have elevated BP. While lifestyle recommendation is recommended for all patients with elevated BP, the re-evaluation time should be 3 to 6 months, not 12 months (Fig. 30-2). The lifetime risk of developing hypertension is higher than 90% (not 50%), and patients with elevated BP have a higher CV risk than those with normal BP values (<120/<80 mm Hg).

9. **A.** Heart rate should be routinely monitored in patients treated with a non-dihydropyridine CCBs because these types of drugs can cause bradycardia due to their ability to block AV node conduction. Serum potassium, sodium, and magnesium do not need to be monitored with CCBs as they do with other medications (eg, thiazide diuretics) because they do not change any electrolytes, including serum calcium. Serum creatinine and BUN should not be altered with CCB therapy as they potentially are with other agents (eg, ACEi, ARB, diuretics), and an electrocardiogram is not necessary as routine monitoring for patients treated with CCBs. See Table 30-10.

10. **A.** Since the patient's BP is not at her goal of <130/80 mm Hg, and because she has a compelling indication of CKD with albuminuria, the dose of the ARB should be optimized to achieve her goal BP and to slow the progression of CKD. Adding a second agent, whether it is hydrochlorothiazide or spironolactone is not necessary at this point, because using the maximum tolerated dose of an ARB (or ACEi as an alternative) is needed because she has albuminuria. The small increase in serum creatinine is less than 30% from the baseline so there is no need to replace olmesartan with carvedilol. See the "Chronic Kidney Disease" section.

11. **D.** Both hydralazine and minoxidil cause direct arteriolar smooth muscle vasodilation, which is their primary mechanism of action that results in BP lowering. This causes a compensatory increase in sympathetic outflow, resulting in an increase in heart rate and sodium and water retention. Using a β-blocker with a diuretic is recommended to block these compensatory actions to mitigate adverse effects. Tachycardia, not bradycardia, is an adverse effect of these agents. Rebound hypertension is not associated with the abrupt cessation of therapy with hydralazine or minoxidil as it is with β-blocker or centrally acting α-agonists. In contrast to centrally acting α-agonists (especially clonidine), anticholinergic side effects are not attributed to hydralazine or minoxidil use. See the "Direct Arterial Vasodilator" section.

12. **D.** Valsartan, an ARB, is the most appropriate to add to the patient's current regimen of verapamil (a non-dihydropyridine CCB). The use of an ARB (or ACEi) with a CCB is a recommended and efficacious antihypertensive combination. Chlorthalidone would not be appropriate due to current hypokalemia, significant kidney dysfunction, and a history of severe gout with hydrochlorothiazide. The patient is already on a non-dihydropyridine CCB and a dihydropyridine CCB (amlodipine) should not be added now. A β-blocker, particularly a non-recommended one such as atenolol, would not be safe in combination with verapamil because it will increase the risk of bradycardia, especially because her current heart rate is 68 beats/min. See Table 30-5 and Box B.

13. **D.** This patient is already on appropriate first-line therapy, a β-blocker, which is proven to reduce both risk of death and recurrent MI in this type of patient with stable ischemic heart disease (his MI was 3 months ago). The preferred add-on agent for this post-MI patient that is already on a β-blocker would be an ACEi or ARB, so adding lisinopril is correct. All of the other options may be helpful in reducing BP to goal, but are not compelling indicated in a patient with stable ischemic heart disease, where β-blocker therapy is the first line, followed by the addition of an ACEi or ARB. See Fig. 30-3.

14. **A.** A history of ischemic stroke (or a transient ischemic attack) is a compelling indication for either a thiazide diuretic as monotherapy or a thiazide with an ACEi when combination therapy is needed. This patient is far from their goal of <130/80 mm Hg, thus requiring >20/10 mm Hg reduction in BP. The preferred therapy, which is compellingly indicated for this patient because of a history of ischemic stroke, is a thiazide with an ACEi. See Fig. 30-3.

15. **C.** Considering the patient has a compelling indication of stable ischemic heart disease (chronic stable angina) and is already on a β-blocker, the next most appropriate therapy to treat both his BP and ischemic chest pain is a non-dihydropyridine CCB. Therefore, adding amlodipine is correct. Adding lisinopril, or irbesartan with hydrochlorothiazide would help lower BP to goal, but will not provide relief of ischemic chest pain. This patient

needs this based on their clinical presentation. Adding diltiazem would be harmful because it would cause significant bradycardia because this patient has a heart rate of 58 beats/min and is already on a β-blocker. See Calcium Channel Blocker (CCB)section.

16. **D.** The side effect of fatigue, particularly as the patient normally exercises 3 times/week, is most likely due to the use of a β-blocker (carvedilol). See β-Blockers section. Heartburn, dry cough, and constipation are common side effects of other types of antihypertensive medications (CCB and ACEi), but not hydrochlorothiazide or carvedilol.

17. **B.** Since the patient is complaining of severe fatigue which is most likely due to the β-blocker, and the fact that her heart rate is 50 beats/min (too low because it is <55), the carvedilol dose should be decreased and another agent added to improve BP control. An ACEi (lisinopril) would be inappropriate and harmful due to a history of ACEi-induced angioedema, so it is contraindicated. Since she also has type 2 diabetes with albuminuria, adding an ARB (irbesartan) is the most appropriate addition. Replacing hydrochlorothiazide with spironolactone and felodipine is not appropriate now because she has compelling indications (diabetes and CKD) that should be treated with an ACEi or ARB. Replacing carvedilol with valsartan would be appropriate for her compelling indication, but would not likely result in her achieving her BP goal of <130/80 mm Hg, and abruptly stopping carvedilol by replacing it with another agent would result in rebound hypertension. See Table 30-5.

18. **D.** None of her current OTC medications are associated with significant increases in BP, so it is safe and appropriate to inform her of this. There is no need to stop these agents, acetaminophen does not increase BP, and though loratadine does not increase BP pseudoephedrine can and should be avoided when possible in patients with uncontrolled hypertension. See Table 30-1.

19. **B.** This patient meets the criteria for resistant hypertension because he is adherent to a drug regimen that includes at least three antihypertensive medications, including a diuretic, long-acting CCB, and ACEi or ARB, all at full doses. Of note, he is also on a fourth agent (a β-blocker). Spironolactone (a mineralocorticoid receptor antagonist) is the most appropriate option for this patient with resistant hypertension and is safe based on his low-normal serum potassium. Adding terazosin, which is an α-blocker, is not reasonable because carvedilol is both an α- and β-blocker. Clonidine is appropriate ahead of a mineralocorticoid receptor antagonist in resistant hypertension and adding chlorthalidone to hydrochlorothiazide is not recommended because they are both similar diuretics. See the "Resistant Hypertension" section.

20. **A.** Because the patient has stage 2 obesity with a calculated BMI of 35.8 kg/m^2, weight loss is appropriate. While increasing potassium dietary intake is advisable, increasing sodium is not; reducing dietary sodium is a recommended and proven lifestyle modification that lowers BP. The patient should start exercising, but should not be advised to go from no exercise to 60 minutes of vigorous exercise most days of the week. This is too rapid of an introduction of exercise and is not likely to be successful. He should also increase, not decrease, his dietary fiber intake as a recommended component of a heart-healthy diet. See Table 30-4 and the "Nonpharmacologic Therapy" section.