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Chapter 10: Hypertension

INTRODUCTION

- *Hypertension* is defined as persistently elevated arterial blood pressure (BP). See **Table 10-1** for the classification of BP in adults.
- Isolated systolic hypertension is diastolic blood pressure (DBP) <80 mm Hg and systolic blood pressure (SBP) ≥130 mm Hg.
- Hypertensive crisis (BP >180/120 mm Hg) is categorized as hypertensive emergency (extreme BP elevation with acute or progressing end-organ damage) or hypertensive urgency (extreme BP elevation without acute or progressing end-organ injury).
- This chapter incorporates elements of 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, the most recent evidence-based U.S. guideline for hypertension management.

TABLE 10-1

Classification of Blood Pressure in Adults

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

PATHOPHYSIOLOGY

- Hypertension may result from an unknown etiology (primary or essential hypertension) or from a specific cause (secondary hypertension). Secondary hypertension (<10% of cases) is usually caused by chronic kidney disease (CKD) or renovascular disease. Other conditions are Cushing syndrome, coarctation of the aorta, obstructive sleep apnea, hyperparathyroidism, pheochromocytoma, primary aldosteronism, and hyperthyroidism. Examples of drugs that may increase BP include corticosteroids, estrogens, nonsteroidal anti-inflammatory drugs (NSAIDs), amphetamines, cyclosporine, tacrolimus, erythropoietin, and venlafaxine.
- Factors contributing to development of primary hypertension include:
  - ✔ Humoral abnormalities involving the renin–angiotensin–aldosterone system (RAAS), natriuretic hormone, and hyperinsulinemia;
  - ✔ Disturbances in the CNS, autonomic nerve fibers, adrenergic receptors, or baroreceptors;
  - ✔ Abnormalities in renal or tissue autoregulatory processes for sodium excretion, plasma volume, and arteriolar constriction;
  - ✔ Deficiency in synthesis of vasodilating substances in vascular endothelium (prostacyclin, bradykinin, nitric oxide) or excess

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vasoconstricting substances (angiotensin II, endothelin I);

✔ High sodium intake or lack of dietary calcium.

- Major causes of death include cerebrovascular events, cardiovascular (CV) events, and renal failure. Probability of premature death correlates with the severity of BP elevation.

CLINICAL PRESENTATION

- Patients with uncomplicated primary hypertension are usually asymptomatic initially.
- Patients with secondary hypertension may have symptoms of the underlying disorder:

✔ Pheochromocytoma—headaches, sweating, tachycardia, palpitations, orthostatic hypotension;

✔ Primary aldosteronism—hypokalemic symptoms of muscle cramps and weakness;

✔ Cushing syndrome—moon face, buffalo hump, hirsutism, weight gain, polyuria, edema, menstrual irregularities, acne, muscle weakness.

DIAGNOSIS

- Elevated BP may be the only sign of primary hypertension on physical examination. Diagnosis should be based on the average of two or more readings taken at each of two or more clinical encounters. Refer to the textbook chapter for the correct procedure for BP measurement.
- Signs of end-organ damage occur primarily in the eyes, brain, heart, kidneys, and peripheral vasculature.
- Funduscopic examination may reveal arteriolar narrowing, focal arteriolar constriction, arteriovenous nicking, retinal hemorrhages and exudates, and disk edema. Presence of papilledema usually indicates a hypertensive emergency requiring rapid treatment.
- Cardiopulmonary examination may reveal abnormal heart rate or rhythm, left ventricular (LV) hypertrophy, coronary artery disease, or heart failure (HF).
- Peripheral vascular examination may reveal aortic or abdominal bruits, distended veins, diminished or absent peripheral pulses, or lower extremity edema.
- Patients with renal artery stenosis may have an abdominal systolic-diastolic bruit.
- Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, blood cells, and casts in the urine may indicate renovascular disease.
- *Laboratory tests*: Blood urea nitrogen (BUN), serum creatinine with estimated glomerular filtration rate (eGFR, using the Modification of Diet in Renal Disease [MDRD] equation), fasting lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium, calcium), uric acid, hemoglobin and hematocrit, and spot urine albumin-to-creatinine ratio. A 12-lead electrocardiogram (ECG) should also be obtained.
- *Laboratory tests to diagnose secondary hypertension*: Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, red blood cells, and casts in the urine may indicate renovascular disease. Obtain plasma norepinephrine and urinary metanephrine levels for pheochromocytoma; plasma and urinary aldosterone concentrations for primary aldosteronism; and plasma renin activity, captopril stimulation test, renal vein renin, and renal artery angiography for renovascular disease.

TREATMENT

- Goals of Treatment: The overall goal is to reduce morbidity and mortality from CV events. The 2017 ACC/AHA guideline recommends a goal BP of <130/80 mm Hg for most patients, including those with clinical arteriosclerotic cardiovascular disease (ASCVD), diabetes, or CKD. For older ambulatory, community-dwelling patients, the goal is SBP <130 mm Hg. For institutionalized older patients and those with a high disease burden

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or limited life expectancy, consider a relaxed SBP goal of <150 mm Hg (or <140 mm Hg if tolerated).

Nonpharmacologic Therapy

- Implement lifestyle modifications in all patients with elevated BP or stage 1 or 2 hypertension. These measures alone are appropriate initial treatment for patients with elevated BP or stage 1 hypertension who are at low risk of ASCVD (ie, primary prevention with a 10-year ASCVD risk <10%). Start drug therapy for these patients when BP is ≥140/90 mm Hg. For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or an elevated 10-year ASCVD risk ≥10%, the threshold for starting drug therapy is ≥130/80 mm Hg with a goal BP of <130/80 mm Hg.
- Lifestyle modifications shown to lower BP include (1) weight loss if overweight or obese, (2) the Dietary Approaches to Stop Hypertension (DASH) eating plan, (3) reduced salt intake, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride), (4) physical activity (90–150 min/week of aerobic or dynamic resistance training), and (5) moderation of alcohol intake (≤2 drinks/day in men and ≤1 drink/day in women). Although smoking cessation does not control BP, it reduces CV disease risk and should be encouraged.

Pharmacologic Therapy

General Approach to Treatment

- Initial drug selection depends on the degree of BP elevation and presence of compelling indications for certain drugs.
- Use a single first-line drug as initial therapy in most patients with newly diagnosed stage 1 hypertension. Start combination drug therapy (preferably with two first-line drugs) as the initial regimen in patients with newly diagnosed stage 2 hypertension (**Fig. 10-1**).
- The four first-line options are **angiotensin-converting enzyme (ACE) inhibitors**, **angiotensin II receptor blockers (ARBs)**, **calcium channel blockers (CCBs)**, and **thiazide diuretics**.
- **β-Blockers** should be reserved to treat a specific compelling indication or in combination with a first-line antihypertensive agent for patients without a compelling indication.
- Other antihypertensive drug classes (**α_1-blockers**, **direct renin inhibitors**, **central α_2-agonists**, and **direct arterial vasodilators**) may be used for select patients after implementing first-line agents. They are generally reserved for resistant hypertension or as add-on therapy with multiple other first-line agents. However, they either lack convincing evidence showing reduced morbidity and mortality in hypertension or have a high incidence of adverse effects that hinders tolerability.

FIGURE 10-1

Algorithm for treatment of elevated BP and hypertension based on BP category at initial diagnosis. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from at least one well-designed clinical trial with randomization, from cohort or case-controlled 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. *Most patients with diabetes or CKD have a 10-year ASCVD risk score ≥10%.

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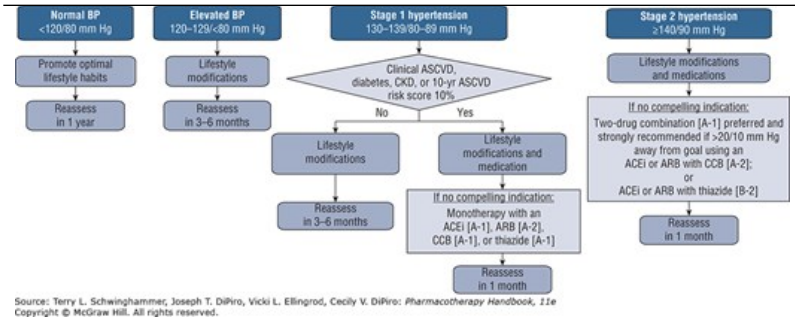

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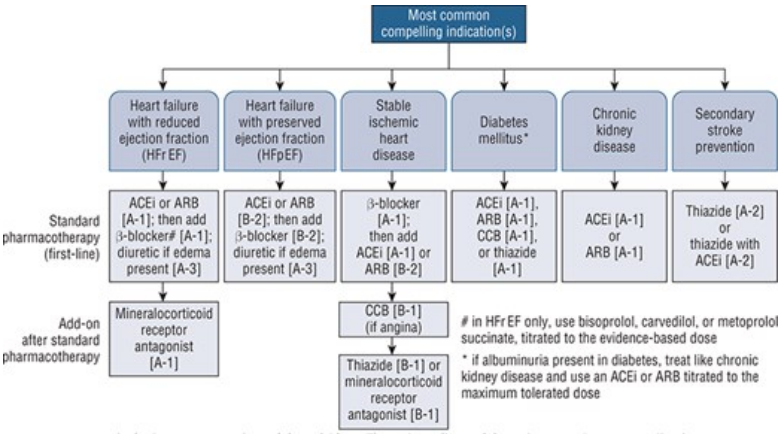
Compelling Indications

- Compelling indications are specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication (**Fig. 10-2**). Selection of drug therapy should follow an evidence-based order.

FIGURE 10-2

Compelling indications for individual drug classes. Recommendations are evidence-based from outcome studies or clinical guidelines. The order of drug therapies is a general guidance that should be balanced with clinical judgment and patient response. Add-on recommendations are used when additional agents are needed to lower BP to goal values. BP control should be managed concurrently with the compelling indication. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one 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.



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Heart Failure with Reduced Ejection Fraction (HFrEF)

- Guideline-directed medical therapy consists of three to four drugs: ACE inhibitor or ARB plus diuretic, followed by addition of an evidence-based β-blocker and possibly a mineralocorticoid receptor antagonist.
- Start an ACE inhibitor or ARB in low doses to avoid orthostatic hypotension because of the high renin state in HF.
- Diuretics reduce edema, and loop diuretics are often needed, especially in patients with advanced HF and/or CKD.
- β-Blockers modify disease in HFrEF and are part of standard treatment; adding a β-blocker to a diuretic with an ACE inhibitor or ARB reduces CV morbidity and mortality. Because of the risk of exacerbating HF, β-blockers must be started in very low doses and titrated slowly to high doses based on tolerability. **Bisoprolol**, **carvedilol**, and **metoprolol succinate** are the only β-blockers proven to be beneficial in HFrEF.

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- After implementation of a standard three-drug regimen, other agents may be added to further reduce CV morbidity and mortality, and reduce BP if needed. A mineralocorticoid receptor antagonist (**spironolactone** or **eplerenone**) may be considered at this point. For African Americans, addition of a fixed-dose combination of **isosorbide dinitrate** and **hydralazine** to the standard three-drug regimen is an option to improve CV outcomes.

Heart Failure with Preserved Ejection Fraction (HFpEF)

- Unlike interventions in HFrEF that decrease morbidity and mortality, trials using the same medications in HFpEF have not shown similar benefits. Therefore, treatment should be targeted at signs and symptoms (eg, dyspnea, fatigue, edema), appropriate management of underlying coronary artery disease, and attainment of goal BP to prevent HF progression.
- Patients should use a β-blocker or an ACE inhibitor (or ARB) for treatment of hypertension, and they should receive a diuretic if signs and symptoms of edema are present.

Stable Ischemic Heart Disease (SIHD)

- β-Blockers (without ISA) are first-line therapy in SIHD; they reduce BP and improve angina symptoms by decreasing myocardial oxygen consumption and demand. β-Blockers should be used for hypertension treatment in patients with SIHD. An ACE inhibitor or ARB has been shown to reduce CV events as an add-on to a β-blocker.
- A long-acting nondihydropyridine CCB is an alternative to a β-blocker in SIHD, but β-blockers are the therapy of choice.
- A dihydropyridine CCB may be considered as add-on therapy in SIHD patients who have ongoing ischemic symptoms, but cardiac stimulation makes these agents less desirable.
- For acute coronary syndromes, first-line therapy includes a β-blocker and ACE inhibitor (or ARB); the combination lowers BP, controls acute ischemia, and reduces CV risk.

Diabetes Mellitus

- All four first-line antihypertensive classes (ACE inhibitors, ARBs, CCBs, thiazides) reduce CV events in patients with diabetes, with no evidence of difference in all-cause mortality, CV mortality, HF, or stroke. 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 creatinine]). Therefore, any first-line agent can be used to control hypertension in patients with diabetes in the absence of albuminuria. Regardless of the initial agent selected, most patients require combination therapy, which typically includes an ACE inhibitor (or ARB) with a CCB or thiazide.
- After first-line agents, a β-blocker is a useful add-on therapy for BP control in patients with diabetes. However, they may mask symptoms of hypoglycemia (tremor, tachycardia, and palpitations but not sweating) in tightly controlled patients, delay recovery from hypoglycemia, and elevate BP due to vasoconstriction caused by unopposed β-receptor stimulation during the hypoglycemic recovery phase. Despite these potential problems, β-blockers can be used safely in patients with diabetes.

Chronic Kidney Disease

- In addition to lowering BP, ACE inhibitors and ARBs reduce intraglomerular pressure, which may further slow CKD progression.
- Start with low doses and evaluate the serum creatinine soon after starting therapy to minimize the risk of rapid and profound BP drops that could precipitate acute kidney injury (AKI).

Secondary Stroke Prevention

- A thiazide diuretic, either alone or combined with an ACE inhibitor, is recommended for patients with history of stroke or transient ischemic attack. Implement antihypertensive drug therapy only after patients have stabilized after an acute cerebrovascular event.

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- The threshold for starting antihypertensive drug therapy in patients with a history of stroke is when BP is >140/90 mm Hg. Once therapy is initiated, patients should be treated to a goal of <130/80 mm Hg.

First-Line Antihypertensive Agents (Table 10-2)

TABLE 10-2

Most Common First-Line and Other Antihypertensive Agents

Class	Subclass	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
ACEi		Benazepril (Lotensin)	10–40	1 or 2
		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
		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
		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
		Felodipine (Plendil)	5–20	1
		Nifedipine long-acting (Afeditab CR Adalat CC, Nifediac CC,	30–90	1

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		Nifedical XL, Procardia XL)		
		Nisoldipine (Sular)	10–40	1
	Nondihydropyridine	Diltiazem sustained release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–480	1
		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 (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
		Furosemide (Lasix)	20–80	2
		Torsemide (Demadex)	5–10	1
	Potassium sparing	Amiloride (Midamor)	5–10	1 or 2
		Amiloride/Hydrochlorothiazide (Moduretic)	5–50	1
		Triamterene (Dyrenium)	50–100	1 or 2
		Triamterene/Hydrochlorothiazide (Dyazide, Maxide)	37.5–75/25–50	1
	Mineralocorticoid receptor antagonist	Eplerenone (Inspra)	50–100	1 or 2
		Spironolactone (Aldactone, CaroSpir)	25–50	1 or 2
β-Blocker	Cardioselective	Atenolol (Tenormin)	25–100	1 or 2
		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

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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

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors block conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion. ACE inhibitors also block degradation of bradykinin and stimulate synthesis of other vasodilating substances (prostaglandin E_2 and prostacyclin).
- Starting doses should be low with slow dose titration. Acute hypotension may occur at the onset of therapy, especially in patients who are sodium or volume depleted, in HF exacerbation, very elderly, or on concurrent vasodilators or diuretics. Starting doses in such patients should be half the normal dose followed by slow dose titration.
- ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. Hyperkalemia occurs primarily in patients with CKD or those also taking potassium supplements, potassium-sparing diuretics, mineralocorticoid receptor antagonists, ARBs, or direct renin inhibitors.
- AKI is an uncommon but serious side effect; preexisting kidney disease increases risk. Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making them particularly susceptible to AKI.
- GFR decreases somewhat when ACE inhibitors are started because of inhibition of angiotensin II vasoconstriction on efferent arterioles. Serum creatinine concentrations often increase, but modest elevations (eg, absolute increases <1 mg/dL [88 µmol/L]) do not warrant treatment changes. Discontinue therapy or reduce dose if larger increases occur.
- Angioedema occurs in <1% of patients. Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation to support respiration. An ARB can generally be used in patients with a history of ACE inhibitor-induced angioedema, with careful monitoring.
- A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.
- ACE inhibitors (as well as ARBs and direct renin inhibitors) are contraindicated in pregnancy.

Angiotensin II Receptor Blockers

- Angiotensin II is generated by the renin–angiotensin pathway (which involves ACE) and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors block only the renin–angiotensin pathway, whereas ARBs inhibit angiotensin II generated by either pathway. The ARBs directly block the angiotensin II type 1 receptor that mediates the effects of angiotensin II.
- Unlike ACE inhibitors, ARBs do not block bradykinin breakdown. Although this accounts for the lack of cough as a side effect, some of the antihypertensive effect of ACE inhibitors may be due to bradykinin.
- The combination of an ACE inhibitor and ARB has no additional CV event lowering but is associated with a higher risk of side effects (renal

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dysfunction, hypotension) and should be avoided.

- All ARBs have similar antihypertensive efficacy and fairly flat dose-response curves. Addition of a CCB or thiazide diuretic significantly increases antihypertensive efficacy.
- ARBs have a low incidence of side effects. Like ACE inhibitors, they may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. ARBs are contraindicated in pregnancy.

Calcium Channel Blockers

- Dihydropyridine and nondihydropyridine CCBs are first-line antihypertensive therapies and are also used in addition to or instead of other first-line agents for the compelling indication of ischemic heart disease.
- CCBs cause relaxation of cardiac and smooth muscle by blocking voltage-sensitive calcium channels, thereby reducing entry of extracellular calcium into cells. This leads to vasodilation and a corresponding reduction in BP. Dihydropyridine CCBs may cause reflex sympathetic activation, and all agents (except **amlodipine** and **felodipine**) may have negative inotropic effects.
- **Verapamil** decreases heart rate, slows atrioventricular (AV) nodal conduction, and produces a negative inotropic effect that may precipitate HF in patients with borderline cardiac reserve. **Diltiazem** decreases AV conduction and heart rate to a lesser extent than verapamil.
- Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia, AV block, and HF. Both can cause peripheral edema and hypotension. Verapamil causes constipation in about 7% of patients.
- Dihydropyridines cause a baroreceptor-mediated reflex increase in heart rate because of potent peripheral vasodilating effects. Dihydropyridines do not decrease AV node conduction and are not effective for treating supraventricular tachyarrhythmias.
- Short-acting nifedipine may rarely increase frequency, intensity, and duration of angina in association with acute hypotension. This effect may be obviated by using sustained-release formulations of nifedipine or other dihydropyridines. Other side effects of dihydropyridines are dizziness, flushing, headache, gingival hyperplasia, and peripheral edema.

Diuretics

- Thiazides are the preferred type of diuretic and are a first-line option for most patients with hypertension. **Chlorthalidone** (thiazide-like) is preferred over **hydrochlorothiazide**, especially in resistant hypertension, because it is more potent on a milligram-per-milligram basis.
- Loop diuretics are more potent for inducing diuresis but are not ideal antihypertensives unless edema treatment is also needed. Loop diuretics are sometimes required over thiazides in patients with severe CKD when eGFR is <30 mL/min/1.73 m^2, especially when edema is present.
- Potassium-sparing diuretics are weak antihypertensives when used alone and provide minimal additive effect when combined with a thiazide or loop diuretic. Their primary use is in combination with another diuretic to counteract potassium-wasting properties.
- Mineralocorticoid receptor antagonists (**spironolactone** and **eplerenone**) are also potassium-sparing diuretics that are usually used to treat resistant hypertension because elevated aldosterone concentrations are prevalent in this setting. They are also used as add-on agents in patients with HFrEF with or without concomitant hypertension.
- Acutely, diuretics lower BP by causing diuresis. The reduction in plasma volume and stroke volume associated with diuresis decreases cardiac output and BP. The initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance. With chronic therapy, extracellular fluid volume and plasma volume return to near pretreatment levels, and peripheral vascular resistance falls below baseline. Reduced peripheral vascular resistance is responsible for persistent hypotensive effects. Thiazides also mobilize sodium and water from arteriolar walls, which may contribute to decreased peripheral vascular resistance and lowered BP.
- Combining diuretics with other antihypertensive agents usually results in an additive hypotensive effect because of independent mechanisms of action. Furthermore, many nondiuretic antihypertensive agents induce sodium and water retention, which is counteracted by concurrent diuretic use.

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- Side effects of thiazides include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction. Loop diuretics have less effect on serum lipids and glucose, but hypokalemia is more pronounced, and hypocalcemia may occur.
- Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps, and severe electrolyte abnormalities may result in serious cardiac arrhythmias. Low-dose therapy (eg, 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) causes less electrolyte disturbances than higher doses.
- Potassium-sparing diuretics may cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with a mineralocorticoid receptor antagonist, ACE inhibitor, ARB, direct renin inhibitor, or potassium supplement. Eplerenone has an increased risk for hyperkalemia and is contraindicated in patients with impaired renal function or type 2 diabetes with proteinuria. Spironolactone may cause gynecomastia in up to 10% of patients; this effect occurs rarely with eplerenone.

Alternative Antihypertensive Agents (Tables 10-2 and 10-3)

TABLE 10-3

Alternative Antihypertensive Agents

Class Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
α_1-Blockers		
Doxazosin (Cardura) Prazosin (Minipress) Terazosin (Hytrin)	1–8 2–20 1–20	1 2 or 3 1 or 2
Direct renin inhibitor		
Aliskiren (Tekturna)	150–300	1
Central α_2-agonists		
Clonidine (Catapres) Clonidine patch (Catapres-TTS) Methyldopa (Aldomet)	0.1–0.8 0.1–0.3 250–1000	2 1 weekly 2
Direct arterial vasodilators		
Minoxidil (Loniten) Hydralazine (Apresoline)	10–40 20–100	1 or 2 2 to 4

β-Blockers

- Evidence suggests that β-blockers may not reduce CV events as well as ACE inhibitors, ARBs, CCBs, or thiazides when used as the initial drug in patients who do not have a compelling indication for a β-blocker.
- β-Blockers are appropriate first-line agents when used to treat specific compelling indications (**Fig. 10-2**) or when an ACE inhibitor, ARB, CCB, or thiazide cannot be used. β-Blockers also have an important role as add-on therapy to first-line agents in patients with hypertension but no compelling indications.

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- Their hypotensive mechanism may involve decreased cardiac output through negative chronotropic and inotropic cardiac effects and inhibition of renin release from the kidney.
- **Atenolol**, **betaxolol**, **bisoprolol**, **metoprolol**, and **nebivolol** are cardioselective at low doses and bind more avidly to β_1-receptors than to β_2-receptors. As a result, they are less likely to provoke bronchospasm and vasoconstriction and are safer than nonselective β-blockers in patients with asthma or diabetes who have a compelling indication for a β-blocker. Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.
- **Acebutolol**, **carteolol**, and **pindolol** possess intrinsic sympathomimetic activity (ISA) or partial β-receptor agonist activity. When sympathetic tone is low, as in resting states, β-receptors are partially stimulated, so resting heart rate, cardiac output, and peripheral blood flow are not reduced when receptors are blocked. Theoretically, these drugs may have advantages in select patients with HF or sinus bradycardia. Unfortunately, they do not reduce CV events as well as other β-blockers and may increase CV risk in patients with SIHD. Thus, agents with ISA are rarely needed and have no role in hypertension management.
- **Atenolol** and **nadolol** have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with renal insufficiency. Even though the half-lives of other β-blockers are shorter, once-daily administration still may be effective.
- Cardiac side effects include bradycardia, AV conduction abnormalities, and acute HF. Blocking β_2-receptors in arteriolar smooth muscle may cause cold extremities and aggravate intermittent claudication or Raynaud phenomenon because of decreased peripheral blood flow. Increases in serum lipids and glucose appear to be transient and of little clinical significance.
- Abrupt cessation of β-blocker therapy can produce cardiac ischemia (angina, chest pain), a CV event, or even death in patients with coronary artery disease. In patients without heart disease, abrupt discontinuation of β-blockers may be associated with tachycardia, sweating, and generalized malaise in addition to increased BP. For these reasons, the dose should always be tapered gradually over 1–2 weeks before discontinuation.

α_1-Receptor Blockers

- **Prazosin**, **terazosin**, and **doxazosin** are selective α_1-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation and BP lowering.
- A first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope may occur within 1–3 hours of the first dose or after later dosage increases. The patient should take the first dose (and subsequent first increased doses) at bedtime. Occasionally, orthostatic hypotension and dizziness persist with chronic administration.
- Sodium and water retention can occur; these agents are most effective when given with a thiazide to maintain antihypertensive efficacy and minimize edema.
- These agents block postsynaptic α_1-adrenergic receptors on the prostate capsule, causing relaxation and decreased resistance to urinary outflow. Although they can provide symptomatic benefit in men with benign prostatic hyperplasia, they should be used to lower BP only in combination with first-line antihypertensive agents.

Direct Renin Inhibitor

- **Aliskiren** blocks the RAAS at its point of activation, resulting in reduced plasma renin activity and BP. It is approved for monotherapy or in combination therapy. It should not be used with an ACE inhibitor or an ARB because of a higher risk of adverse effects without additional reduction in CV events. Its role in the management of hypertension is limited.
- Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to aliskiren. It is contraindicated in pregnancy due to known teratogenic effects.

Central α_2-Agonists

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- **Clonidine, guanfacine**, and **methyldopa** lower BP primarily by stimulating α_2-adrenergic receptors in the brain, which reduces sympathetic outflow from the vasomotor center and increases vagal tone. Stimulation of presynaptic α_2-receptors peripherally may contribute to reduced sympathetic tone. Consequently, there may be decreases in heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.
- Clonidine is often used in resistant hypertension, and methyldopa is frequently used for pregnancy-induced hypertension.
- Chronic use results in sodium and fluid retention. Other side effects include depression, orthostatic hypotension, dizziness, and anticholinergic effects (eg, dry mouth, sedation).
- Abrupt cessation may lead to rebound hypertension, perhaps from a compensatory increase in norepinephrine release that follows discontinuation of presynaptic α-receptor stimulation.
- Methyldopa rarely causes hepatitis or hemolytic anemia. A transient elevation in hepatic transaminases occasionally occurs. Discontinue therapy if persistent increases in liver function tests occur, because this may herald onset of fulminant, life-threatening hepatitis. Coombs-positive hemolytic anemia occurs rarely, and 20% of patients exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited usefulness except in pregnancy.

Direct Arterial Vasodilators

- **Hydralazine** and **minoxidil** directly relax arteriolar smooth muscle, resulting in vasodilation and BP lowering. Compensatory activation of baroreceptor reflexes increases sympathetic outflow, thereby increasing heart rate, cardiac output, and renin release. Consequently, hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a diuretic and a β-blocker. The diuretic minimizes the side effect of sodium and water retention. Direct vasodilators can precipitate angina in patients with underlying SIHD unless the baroreceptor reflex mechanism is blocked with a β-blocker. Nondihydropyridine CCBs can be used as an alternative to β-blockers in patients with contraindications to β-blockers.
- Hydralazine may cause a dose-related, reversible lupus-like syndrome, which is more common in slow acetylators. Lupus-like reactions can usually be avoided by limiting the maximum total daily dose to 200 mg. Because of side effects, hydralazine has limited usefulness for chronic hypertension management.
- Minoxidil is a more potent vasodilator than hydralazine, and compensatory increases in heart rate, cardiac output, renin release, and sodium retention are more dramatic. Due to significant water retention, a loop diuretic is often more effective than a thiazide. Reversible hypertrichosis on the face, arms, back, and chest may be troublesome. Minoxidil is reserved for resistant hypertension and for patients requiring hydralazine who experience drug-induced lupus.

Special Populations

Older Persons

- Older patients may present with either isolated systolic hypertension or elevation in both SBP and DBP. CV morbidity and mortality are more directly correlated to SBP than to DBP in patients aged 50 and older.
- First-line antihypertensives provide significant benefits and can be used safely in older patients, but smaller-than-usual initial doses must be used for initial therapy.
- Although the most appropriate BP goal for older patients has been debated, the totality of evidence indicates that older ambulatory patients should be treated to an SBP goal of <130 mm Hg, with careful monitoring. In patients with multiple comorbidities, a relaxed SBP goal of at least <150 mm Hg (or <140 mm Hg if tolerated) may be considered.

Children and Adolescents

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- In children, hypertension is defined as SBP or DBP that is >95th percentile for sex, age, and height on at least three occasions. For adolescents, BP values between the 90th and 95th percentile, or >120/80 mm Hg, is considered elevated BP.
- Because secondary hypertension is more common in children and adolescents than in adults, an appropriate workup is required if elevated BP is identified.
- Nonpharmacologic treatment (eg, weight loss if overweight or obese, healthy diet, physical activity) is the cornerstone of therapy for primary hypertension.
- The goal is to reduce the BP to <90th percentile for sex, age, and height and <130/80 mm Hg in adolescents age 13 years and older.
- ACE inhibitors, ARBs, β-blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.
- ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated in sexually active girls because of potential teratogenic effects.

Pregnancy

- *Preeclampsia* is defined as hypertension (elevated BP ≥140/90 mm Hg on more than 2 occasions at least 4 hours apart after 20 weeks' gestation or ≥160/110 mm Hg confirmed within a short interval) in association with 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* is the onset of convulsions in preeclampsia and is a medical emergency.
- Definitive treatment of preeclampsia is delivery, and labor induction is indicated if eclampsia is imminent or present. Otherwise, management consists of restricting activity, bed rest, and close monitoring. Salt restriction or other measures that contract blood volume should be avoided. Antihypertensives are used before induction of labor if DBP is >105 mm Hg, with a target DBP of 95–105 mm Hg. Intravenous (IV) hydralazine is most commonly used; IV labetalol is also effective.
- *Chronic hypertension* is hypertension that predates pregnancy. Labetalol, long-acting nifedipine, or methyldopa is recommended as first-line therapy due to favorable safety profiles. β-Blockers (except atenolol) and CCBs are also reasonable alternatives. ACE inhibitors, ARBs, and the direct renin inhibitor aliskiren are known teratogens and contraindicated in pregnancy.

African Americans

- Hypertension is more common and more difficult to control in African Americans than in those of other races; treatment usually requires two or more antihypertensives to reach a BP goal of <130/80 mm Hg.
- CCBs and thiazides are most effective in African Americans and should be first-line in the absence of a compelling indication. Antihypertensive response is significantly increased when either class is combined with a β-blocker, ACE inhibitor, or ARB, perhaps due to the low-renin pattern of hypertension in African Americans.
- Medications recommended for specific compelling indications should be used, 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 African Americans with SIHD).

Pulmonary Disease and Peripheral Arterial Disease

- Although β-blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and COPD because of fear of inducing bronchospasm, cardioselective β-blockers can be used safely. Consequently, cardioselective agents should be used to treat a compelling indication (ie, SIHD or HF) in patients with reactive airway disease.
- Because PAD is a noncoronary form of ASCVD, patients with PAD are at increased risk of stroke and CV events. β-Blockers can theoretically be problematic because of possible decreased peripheral blood flow secondary to unopposed stimulation of α_1-receptors that results in vasoconstriction. However, available data indicate that β-blockers do not worsen claudication symptoms or cause functional impairment. Therefore, antihypertensive treatment for patients with PAD should follow the same general principles as patients without PAD.

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Hypertensive Urgencies and Emergencies

- *Hypertensive urgencies* are ideally managed by adjusting maintenance therapy, adding a new antihypertensive, increasing the dose of a current medication, or treating anxiety as applicable. Acute administration of a short-acting oral drug (**captopril**, **clonidine**, or **labetalol**) followed by careful observation for several hours to ensure a gradual BP reduction is an option.

  ✔ Captopril 25–50 mg orally may be given at 1- to 2-hour intervals. The onset of action is 15–30 minutes.

  ✔ For treatment of hypertensive rebound after withdrawal of clonidine, 0.2 mg orally is given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg has been administered; a single dose may be sufficient.

  ✔ Labetalol 200–400 mg orally can be given, followed by additional doses every 2–3 hours.

- *Hypertensive emergencies* require immediate BP reduction with a parenteral agent to limit new or progressing end-organ damage. The rate of BP reduction depends on whether the patient has aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma with hypertensive crisis. In these life-threatening situations, patients should be managed in an intensive care unit, and SBP should be reduced immediately to <140 mm Hg in the first hour, with additional SBP lowering to <120 mm Hg for patients with aortic dissection. For patients with a hypertensive emergency without aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma with hypertensive crisis, the initial target is reduction in mean arterial pressure of up to 25% over the first hour. If the patient is then stable, BP can be reduced to 160/100–110 mm Hg within the next 2–6 hours. Precipitous drops in BP may cause end-organ ischemia or infarction. If BP reduction is well tolerated, additional gradual decreases toward the goal BP can be attempted after 24–48 hours.

  ✔ Nitroprusside is the agent of choice for minute-to-minute control in most cases. In aortic dissection, propranolol should be given first to prevent reflex sympathetic activation. When the nitroprusside infusion must be continued longer than 72 hours, measure serum thiocyanate levels, and discontinue the infusion if the level exceeds 12 mg/dL (~2.0 mmol/L). The risk of thiocyanate toxicity is increased in patients with impaired kidney function. Other adverse effects are nausea, vomiting, muscle twitching, and sweating.

  ✔ Dosing guidelines and adverse effects of parenteral agents for treating hypertensive emergency are listed in **Table 10-4**.

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TABLE 10-4

Parenteral Antihypertensive Agents for Hypertensive Emergency

Drug	Dose	Onset (Minutes)	Duration (Minutes)	Adverse Effects
Clevidipine	1–2 mg/hr (32 mg/hr max)	2–4	5–15	Headache, nausea, tachycardia, hypertriglyceridemia
Enalaprilat	1.25–5 mg IV every 6 hours	15–30	360–720	Precipitous fall in BP in high-renin states; variable response
Esmolol hydrochloride	250–500 mcg/kg/min IV bolus, then 50–100 mcg/kg/min IV infusion; may repeat bolus after 5 min or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure
Fenoldopam mesylate	0.1–0.3 mcg/kg/min IV infusion	<5	30	Tachycardia, headache, nausea, flushing
Hydralazine hydrochloride	12–20 mg IV	10–20	60–240	Tachycardia, flushing, headache, vomiting, aggravation of angina
	10–50 mg IM	20–30	240–360	
Labetalol hydrochloride	20–80 mg IV bolus every 10 min; 0.5–2 mg/min IV infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension
Nicardipine hydrochloride	5–15 mg/hr IV	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis
Nitroglycerin	5–100 mcg/min IV infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Sodium nitroprusside	0.25–10 mcg/kg/min IV infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication

BP, blood pressure; IM, intramuscular; IV, intravenous.

EVALUATION OF THERAPEUTIC OUTCOMES

- Both clinic-based and self-measurement home BP monitoring are important for monitoring and managing hypertension. Encourage patients to obtain a home BP monitor, record the results, and bring them to follow-up clinic visits.
- Evaluate BP response in the clinic 4 weeks after initiating or making changes in therapy and compare the results to home BP readings. Once goal BP is obtained, monitor BP every 3–6 months, assuming no signs or symptoms of acute end-organ damage. Evaluate more frequently in patients

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with a history of poor control, nonadherence, progressive end-organ damage, or symptoms of adverse drug effects.

- Automated BP monitoring can be useful to establish effective 24-hour control and confirm white coat or masked uncontrolled hypertension.
- Monitor patients routinely for adverse drug events, which may require dosage reduction or substitution with an alternative antihypertensive agent. Perform laboratory monitoring 4 weeks after starting a new agent or dose increase, and then every 6–12 months in stable patients. For patients treated with a mineralocorticoid receptor antagonist (eplerenone or spironolactone) monitor potassium concentrations and kidney function within 3 days of initiation and again at 1 week to detect potential hyperkalemia.
- Monitor patients for signs and symptoms of hypertension-associated complications. Take 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.
- Monitor funduscopic changes on eye examination, LV hypertrophy on ECG, albuminuria, and changes in kidney function periodically.
- Assess patient adherence with the regimen regularly. Ask patients about changes in their general health perception, physical functioning, and overall satisfaction with treatment.

See Chapter 30, Hypertension, authored by Eric J. MacLaughlin and Joseph J. Saseen, for a more detailed discussion of this topic.

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