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Introduction

Hypertension is sustained elevation of resting systolic BP (≥ 140 mm Hg), diastolic BP (≥ 90 mm Hg), or both.

Hypertension with no known cause (primary; formerly, essential hypertension) is most common. Hypertension with an identified cause (secondary hypertension) is usually due to a renal disorder. Usually, no symptoms develop unless hypertension is severe or long-standing. Diagnosis is by sphygmomanometry. Tests may be done to determine cause, assess damage, and identify other cardiovascular risk factors. Treatment involves lifestyle changes and drugs, including diuretics, β -blockers, ACE inhibitors, angiotensin II receptor blockers, and Ca channel blockers.

(See also [The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure \[JNC 7\]](#).)

In the US, about 65 million people have hypertension. Only about 70% of these people are aware that they have hypertension, only 59% are being treated, and only 34% have adequately controlled BP. In adults, hypertension occurs more often in blacks (32%) than in whites (23%) or Mexican Americans (23%), and morbidity and mortality are greater in blacks.

BP increases with age. About $\frac{2}{3}$ of people > 65 have hypertension, and people with a normal BP at age 55 have a 90% lifetime risk of developing hypertension. Because hypertension becomes so common with age, the age-related increase in BP may seem innocuous, but higher BP increases morbidity and mortality risk. Hypertension may develop during pregnancy (see [Pregnancy Complicated by Disease: Hypertension in Pregnancy](#) and see [Abnormalities of Pregnancy: Preeclampsia and Eclampsia](#)).

Etiology

Hypertension may be primary (85 to 95% of cases) or secondary.

Primary hypertension: Hemodynamics and physiologic components (eg, plasma volume, activity of the renin angiotensin system) vary, indicating that primary hypertension is unlikely to have a single cause. Even if one factor is initially responsible, multiple factors are probably involved in sustaining elevated BP (the mosaic theory). In afferent systemic arterioles, malfunction of ion pumps on sarcolemmal membranes of smooth muscle cells may lead to chronically increased vascular tone. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (eg, dietary Na, obesity, stress) seem to affect only genetically susceptible people.

Secondary hypertension: Causes include renal parenchymal disease (eg, chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders, obstructive uropathy), renovascular disease (see [Arterial Hypertension: Renovascular](#)

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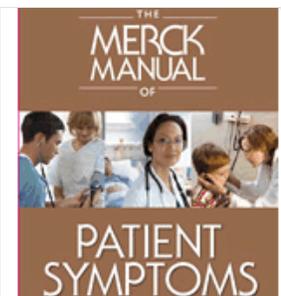
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Hypertension), pheochromocytoma, Cushing's syndrome, primary aldosteronism, congenital adrenal hyperplasia, hyperthyroidism, myxedema, and coarctation of the aorta. Excessive alcohol intake and use of oral contraceptives are common causes of curable hypertension. Use of sympathomimetics, NSAIDs, corticosteroids, cocaine, or licorice commonly contributes to hypertension.

Pathophysiology

Because BP equals cardiac output (CO) × total peripheral vascular resistance (TPR), pathogenic mechanisms must involve increased CO, increased TPR, or both.

In most patients, CO is normal or slightly increased, and TPR is increased. This pattern is typical of primary hypertension and hypertension due to pheochromocytoma, primary aldosteronism, renovascular disease, and renal parenchymal disease.

In other patients, CO is increased (possibly because of venoconstriction in large veins), and TPR is inappropriately normal for the level of CO. Later in the disorder, TPR increases and CO returns to normal, probably because of autoregulation. Some disorders that increase CO (thyrotoxicosis, arteriovenous fistula, aortic regurgitation), particularly when stroke volume is increased, produce isolated systolic hypertension. Some elderly patients have isolated systolic hypertension with normal or low CO, probably due to inelasticity of the aorta and its major branches. Patients with high, fixed diastolic pressures often have decreased CO.

Plasma volume tends to decrease as BP increases; rarely, plasma volume remains normal or increases. Plasma volume tends to be high in hypertension due to primary aldosteronism or renal parenchymal disease and may be quite low in hypertension due to pheochromocytoma. Renal blood flow gradually decreases as diastolic BP increases and arteriolar sclerosis begins. GFR remains normal until late in the disorder; as a result, the filtration fraction is increased. Coronary, cerebral, and muscle blood flow is maintained unless severe atherosclerosis coexists in these vascular beds.

Abnormal Na transport: In many cases of hypertension, Na transport across the cell wall is abnormal, because the Na-K pump (Na⁺, K⁺-ATPase) is defective or inhibited or because permeability to Na⁺ is increased. The result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Ca follows Na, so accumulation of intracellular Ca may be responsible for the increased sensitivity. Because Na⁺, K⁺-ATPase may pump norepinephrine back into sympathetic neurons (thus inactivating this neurotransmitter), inhibition of this mechanism could also enhance the effect of norepinephrine, increasing BP. Defects in Na transport may occur in normotensive children of hypertensive parents.

Sympathetic nervous system: Sympathetic stimulation increases BP, usually more in patients with prehypertension (BP 120 to 139/80 to 89 mm Hg) or hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or both) than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system or in the myocardium and vascular smooth muscle is unknown. A high resting pulse rate, which may result from increased sympathetic nervous activity, is a well-known predictor of hypertension. In some hypertensive patients, circulating plasma catecholamine levels during rest are higher than normal.

Renin-angiotensin-aldosterone system: This system helps regulate blood volume and therefore BP. Renin, an enzyme formed in the juxtaglomerular apparatus, catalyzes conversion of angiotensinogen to angiotensin I. This inactive product is cleaved by ACE, mainly in the lungs but also in the kidneys and brain, to angiotensin II, a potent vasoconstrictor that also stimulates autonomic centers in the brain to increase sympathetic discharge and stimulates release of aldosterone and ADH. Aldosterone and ADH cause Na and water retention, elevating BP. Aldosterone also enhances K excretion; low plasma K (< 3.5 mEq/L) increases vasoconstriction through closure of K channels. Angiotensin III, present in the circulation stimulates aldosterone release as actively as angiotensin II but has

much less pressor activity. Because chymase enzymes also convert angiotensin I to angiotensin II, drugs that inhibit ACE do not fully suppress angiotensin II production.

Renin secretion is controlled by at least 4 mechanisms, which are not mutually exclusive: (1) A renal vascular receptor responds to changes in tension in the afferent arteriolar wall; (2) a macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule; (3) circulating angiotensin has a negative feedback effect on renin secretion; and (4) via the renal nerve, the sympathetic nervous system stimulates renin secretion mediated by β -receptors.

Angiotensin is generally acknowledged to be responsible for renovascular hypertension, at least in the early phase, but the role of the renin-angiotensin-aldosterone system in primary hypertension is not established. However, in black and elderly patients with hypertension, renin levels tend to be low. The elderly also tend to have low angiotensin II levels.

Hypertension due to chronic renal parenchymal disease (renoprival hypertension) results from combination of a renin-dependent mechanism and a volume-dependent mechanism. In most cases, increased renin activity is not evident in peripheral blood. Hypertension is typically moderate and sensitive to Na and water balance.

Vasodilator deficiency: Deficiency of a vasodilator (eg, bradykinin, nitric oxide) rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause hypertension. If the kidneys do not produce adequate amounts of vasodilators (because of renal parenchymal disease or bilateral nephrectomy), BP can increase. Vasodilators and vasoconstrictors (mainly endothelin) are also produced in endothelial cells. Therefore, endothelial dysfunction greatly affects BP.

Pathology and complications: No pathologic changes occur early in hypertension. Severe or prolonged hypertension damages target organs (primarily the cardiovascular system, brain, and kidneys), increasing risk of coronary artery disease (CAD), MI, stroke (particularly hemorrhagic), and renal failure. The mechanism involves development of generalized arteriolosclerosis and acceleration of atherogenesis (see [Arteriosclerosis](#)). Arteriolosclerosis is characterized by medial hypertrophy, hyperplasia, and hyalinization; it is particularly apparent in small arterioles, notably in the eyes and the kidneys. In the kidneys, the changes narrow the arteriolar lumen, increasing TPR; thus, hypertension leads to more hypertension. Furthermore, once arteries are narrowed, any slight additional shortening of already hypertrophied smooth muscle reduces the lumen to a greater extent than in normal-diameter arteries. These effects may explain why the longer hypertension has existed, the less likely specific treatment (eg, renovascular surgery) for secondary causes is to restore BP to normal.

Because of increased afterload, the left ventricle gradually hypertrophies, causing diastolic dysfunction. The ventricle eventually dilates, causing dilated cardiomyopathy and heart failure (HF) due to systolic dysfunction. Thoracic aortic dissection is typically a consequence of hypertension; almost all patients with abdominal aortic aneurysms have hypertension.

Symptoms and Signs

Hypertension is usually asymptomatic until complications develop in target organs. Dizziness, flushed facies, headache, fatigue, epistaxis, and nervousness are not caused by uncomplicated hypertension. Severe hypertension (hypertensive emergencies—see [Arterial Hypertension: Hypertensive Emergencies](#)) can cause severe cardiovascular, neurologic, renal, and retinal symptoms (eg, symptomatic coronary atherosclerosis, HF, hypertensive encephalopathy, renal failure).

A 4th heart sound is one of the earliest signs of hypertensive heart disease.

Retinal changes may include arteriolar narrowing, hemorrhages, exudates, and, with encephalopathy, papilledema (see [Retinal Disorders: Hypertensive Retinopathy](#)). Changes are classified (according to the Keith, Wagener, and Barker classification) into 4 groups with

increasingly worse prognosis: constriction of arterioles only (grade 1), constriction and sclerosis of arterioles (grade 2), hemorrhages and exudates in addition to vascular changes (grade 3), and papilledema (grade 4).

Diagnosis

- Multiple measurements of BP to confirm
- Urinalysis and urinary albumin:creatinine ratio; if abnormal, consider renal ultrasonography
- Blood tests: Fasting lipids, creatinine, K
- If creatinine increased, renal ultrasonography
- If K decreased, evaluate for aldosteronism
- ECG: If left ventricular hypertrophy, consider echocardiography
- Sometimes thyroid-stimulating hormone measurement
- If BP elevation sudden and labile or severe, evaluate for pheochromocytoma

Hypertension is diagnosed and classified by sphygmomanometry. History, physical examination, and other tests help identify etiology and determine whether target organs are damaged.

BP must be measured twice—first with the patient supine or seated, then after the patient has been standing for ≥ 2 min—on 3 separate days. The average of these measurements is used for diagnosis. BP is classified as normal, prehypertension, or stage 1 (mild) or stage 2 hypertension (see Table 1: [Arterial Hypertension: JNC 7 Classification of Blood Pressure in Adults](#)). Normal BP is much lower for infants and children (see [Approach to the Care of Normal Infants and Children: Blood pressure](#)).

Ideally, BP is measured after the patient rests > 5 min and at different times of day. A BP cuff is applied to the upper arm. An appropriately sized cuff covers $\frac{2}{3}$ of the biceps; the bladder is long enough to encircle $> 80\%$ of the arm, and bladder width equals at least 40% of the arm's circumference. Thus, obese patients require large cuffs. The health care practitioner inflates the cuff above the expected systolic pressure and gradually releases the air while listening over the brachial artery. The pressure at which the first heartbeat is heard as the pressure falls is systolic BP. Disappearance of the sound marks diastolic BP. The same principles are followed to measure BP in a forearm (radial artery) and thigh (popliteal artery).

Sphygmomanometers that contain mercury are most accurate. Mechanical devices should be calibrated periodically; automated readers are often inaccurate.

BP is measured in both arms; if BP in one arm is much higher, the higher value is used. BP is also measured in a thigh (with a much larger cuff) to rule out coarctation of the aorta, particularly in patients with diminished or delayed femoral pulses; with coarctation, BP is significantly lower in the legs. If BP is in the low hypertensive range or is markedly labile, more BP measurements are desirable. BP measurements may be sporadically high before hypertension becomes sustained; this phenomenon probably accounts for "white coat hypertension," in which BP is elevated when measured in the physician's office but normal when measured at home or by ambulatory BP monitoring. (See the Agency for Healthcare Research and Quality's Evidence Report/Technology Assessment summary on the [Utility of](#)

Table 1

JNC 7 Classification of Blood Pressure in Adults

Classification	BP (mm Hg)
Normal	$< 120/80$
Prehypertension	120–139/80–89
Stage 1	140–159 (systolic) or 90–99 (diastolic)
Stage 2	≥ 160 (systolic) or ≥ 100 (diastolic)

JNC = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

[Blood Pressure Monitoring Outside of the Clinic Setting.](#)) However, extreme BP elevation alternating with normal readings is unusual and possibly suggests pheochromocytoma or unacknowledged drug use.

History: The history includes the known duration of hypertension and previously recorded levels; any history or symptoms of CAD, HF, or other relevant coexisting disorders (eg, stroke, renal dysfunction, peripheral arterial disease, dyslipidemia, diabetes, gout); and a family history of any of these disorders. Social history includes exercise levels and use of tobacco, alcohol, and stimulant drugs (prescribed and illicit). A dietary history focuses on intake of salt and stimulants (eg, tea, coffee, caffeine-containing sodas, energy drinks).

Physical examination: The physical examination includes measurement of height, weight, and waist circumference; funduscopic examination (see [Retinal Disorders: Symptoms, Signs, and Diagnosis](#)) for retinopathy; auscultation for bruits in the neck and abdomen; and a full cardiac, respiratory, and neurologic examination. The abdomen is palpated for kidney enlargement and abdominal masses. Peripheral arterial pulses are evaluated; diminished or delayed femoral pulses suggest aortic coarctation, particularly in patients < 30.

Testing: The more severe the hypertension and the younger the patient, the more extensive is the evaluation. Generally, when hypertension is newly diagnosed, routine testing to detect target-organ damage and cardiovascular risk factors is done. Tests include urinalysis, spot urine albumin:creatinine ratio, blood tests (creatinine, K, Na, fasting plasma glucose, lipid profile), and ECG. Thyroid-stimulating hormone is often measured. Ambulatory BP monitoring, renal radionuclide imaging, chest x-ray, screening tests for pheochromocytoma, and renin-Na profiling are not routinely necessary. Peripheral plasma renin activity is not helpful in diagnosis or drug selection.

Depending on results of initial tests and examination, other tests may be needed. If urinalysis detects albuminuria (proteinuria), cylindruria, or microhematuria or if serum creatinine is elevated (≥ 1.4 mg/dL in men; ≥ 1.2 mg/dL in women), renal ultrasonography to evaluate kidney size may provide useful information. Patients with hypokalemia unrelated to diuretic use are evaluated for primary aldosteronism (see [Adrenal Disorders: Primary Aldosteronism](#)) and high salt intake.

On ECG, a broad, notched P-wave indicates atrial hypertrophy and, although nonspecific, may be one of the earliest signs of hypertensive heart disease. Left ventricular hypertrophy, indicated by a sustained apical thrust and abnormal QRS voltage with or without evidence of ischemia, may occur later. If either of these findings is present, echocardiography is often done. In patients with an abnormal lipid profile or symptoms of CAD, tests for other cardiovascular risk factors (eg, C-reactive protein) may be useful.

If coarctation of the aorta is suspected, chest x-ray, echocardiography, CT, or MRI helps confirm the diagnosis.

Patients with labile, significantly elevated BP and symptoms such as headache, palpitations, tachycardia, excessive perspiration, tremor, and pallor are screened for pheochromocytoma (eg, by measuring plasma free metanephrines—see [Adrenal Disorders: Diagnosis](#)).

Patients with symptoms suggesting Cushing's syndrome, a connective tissue disorder, eclampsia, acute porphyria, hyperthyroidism, myxedema, acromegaly, or CNS disorders are evaluated (see elsewhere in The Manual).

Prognosis

The higher the BP and the more severe the retinal changes and other evidence of target-organ involvement, the worse is the prognosis. Systolic BP predicts fatal and nonfatal cardiovascular events better than diastolic BP. Without treatment, 1-yr survival is < 10% in patients with retinal sclerosis, cotton-wool exudates, arteriolar narrowing, and hemorrhage (grade 3 retinopathy), and < 5% in patients with the same changes plus papilledema (grade 4 retinopathy). CAD is the most common cause of death among treated hypertensive

patients. Ischemic or hemorrhagic stroke is a common consequence of inadequately treated hypertension. However, effective control of hypertension prevents most complications and prolongs life.

General Treatment

- Weight loss and exercise
- Smoking cessation
- Diet: Increased fruits and vegetables, decreased salt, limited alcohol
- Drugs if BP is initially high (> 160/100) or unresponsive to lifestyle modifications

Primary hypertension has no cure, but some causes of secondary hypertension can be corrected. In all cases, control of BP can significantly limit adverse consequences. Despite the theoretical efficacy of treatment, BP is lowered to the desired level in only $\frac{1}{3}$ of hypertensive patients in the US.

For all patients, treatment aims to reduce BP to < 140/90 mm Hg; for those with a kidney disorder or diabetes, the goal is < 130/80 mm Hg or as near this level as tolerated. Even the elderly and frail elderly can tolerate a diastolic BP as low as 60 to 65 mm Hg well and without an increase in cardiovascular events. Ideally, patients or family members measure BP at home, provided they have been trained to do so, they are closely monitored, and the sphygmomanometer is regularly calibrated. Treatment of hypertension during pregnancy requires special considerations because some antihypertensive drugs can harm the fetus (see [Pregnancy Complicated by Disease: Diagnosis and Treatment](#)).

Lifestyle modifications: Recommendations include regular aerobic physical activity at least 30 min/day most days of the week; weight loss to a body mass index of 18.5 to 24.9 (see the Cochrane review abstract [Dieting to reduce body weight for controlling hypertension in adults](#)); smoking cessation; a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat content; dietary sodium [Na⁺] of < 2.4 g/day (< 6 g NaCl); and alcohol consumption of ≤ 1 oz/day in men and ≤ 0.5 oz/day in women. (See the National Heart Lung and Blood Institute's [Dietary Approaches to Stop Hypertension \[DASH\] Eating Plan](#).) In stage 1 (mild) hypertension with no signs of target-organ damage, lifestyle changes may make drugs unnecessary. Patients with uncomplicated hypertension do not need to restrict their activities as long as BP is controlled. Dietary modifications can also help control diabetes, obesity, and dyslipidemias. Patients with prehypertension are encouraged to follow these lifestyle recommendations.

Drugs: If systolic BP remains > 140 mm Hg or diastolic BP remains > 90 mm Hg after 6 mo of lifestyle modifications, antihypertensive drugs are required. Unless hypertension is severe, drugs are usually started at low doses. Drugs are initiated simultaneously with lifestyle changes for all patients with prehypertension or hypertension plus diabetes, a kidney disorder, target-organ damage, or cardiovascular risk factors and for those with an initial BP of > 160/100 mm Hg. Signs of hypertensive emergencies require immediate BP reduction with parenteral antihypertensives.

For most hypertensive patients, one drug, usually a thiazide-type diuretic, is given initially. Depending on the patient's characteristics and coexisting disorders, other drugs can be used initially or added to the thiazide. Low-dose [aspirin](#) (81 mg once/day) appears to reduce incidence of cardiac events in hypertensive patients and is recommended when tolerated and not contraindicated.

Some antihypertensives are contraindicated in certain disorders (eg, β -blockers in asthma) or are indicated particularly for certain disorders (eg, β -blockers or Ca channel blockers for angina pectoris, ACE inhibitors or angiotensin II receptor blockers for diabetes or proteinuria—see Table 2: [Arterial Hypertension: Choice of Antihypertensive Drug Class](#)  and Table 3: [Arterial Hypertension: Antihypertensives for High-Risk Patients](#) ). When a single drug is used, black men may respond best to a Ca channel blocker (eg, [diltiazem](#) ). Thiazide-type diuretics appear to be particularly effective in people > 60 and in blacks.

If the initial drug is ineffective or has intolerable adverse effects, another drug can be substituted. If the initial drug is only partly effective but well tolerated, the dose can be increased or a second drug with a different mechanism added.

If initial systolic BP is > 160 mm Hg, 2 drugs are often used. Options include combining a diuretic with a β -blocker, an ACE inhibitor, or an angiotensin II receptor blocker and combining a Ca channel blocker with an ACE inhibitor or an angiotensin II receptor blocker. An appropriate combination and dose are determined; many are available as single tablets, which improve compliance (see Table 4: [Arterial Hypertension: Combination Drugs Used for Hypertension](#) ). For severe or refractory hypertension, 3 or 4 drugs may be necessary.

Table 3**Antihypertensives for High-Risk Patients**

Coexisting Condition	Drug Classes
Heart failure	ACE inhibitors
	Angiotensin II receptor blockers
	β -Blockers
	K-sparing diuretics
	Other diuretics
Post-MI	β -Blockers
	ACE inhibitors
	K-sparing diuretics
Cardiovascular risk factors	β -Blockers
	ACE inhibitors
	Diuretics
	Ca channel blockers
Diabetes	Diuretics
	β -Blockers
	ACE inhibitors
	Angiotensin II receptor blockers
	Ca channel blockers
Chronic kidney disorders	ACE inhibitors
	Angiotensin II receptor blockers
Risk of recurrent stroke	ACE inhibitors
	Diuretics

Table 4**Combination Drugs Used for Hypertension**

Classes	Drugs	Available Strengths (mg/mg)
Diuretic/diuretic	Triamterene/hydrochlorothiazide	37.5/25, 50/25, 75/50
	Spironolactone/hydrochlorothiazide	25/25, 50/50
	Amiloride/hydrochlorothiazide	5/50
β -Blocker/diuretic	Propranolol/hydrochlorothiazide	40/25, 80/25
	Metoprolol/hydrochlorothiazide	50/25, 100/25
	Atenolol/chlorthalidone	50/25, 100/25
	Nadolol/bendroflumethiazide	40/5, 80/5
	Timolol/hydrochlorothiazide	10/25
	Propranolol LA (long acting)/hydrochlorothiazide	80/50, 120/50, 160/50
	Bisoprolol/hydrochlorothiazide	2.5/6.25, 5/6.25, 10/6.25

Adrenergic inhibitor/diuretic	Guanethidine/hydrochlorothiazide	10/25
	Methyldopa/hydrochlorothiazide	250/15, 250/25, 500/30, 500/50
	Methyldopa/chlorothiazide	250/150, 250/250
	Reserpine/chlorothiazide	0.125/250, 0.25/500
	Reserpine/chlorthalidone	0.125/25, 0.25/50
	Reserpine/hydrochlorothiazide	0.125/25, 0.125/50
	Clonidine/chlorthalidone	0.1/15, 0.2/15, 0.3/15
ACE inhibitor/diuretic	Captopril/hydrochlorothiazide	25/15, 25/25, 50/15, 50/25
	Enalapril/hydrochlorothiazide	5/12.5, 10/25
	Lisinopril/hydrochlorothiazide	10/12.5, 20/12.5, 20/25
	Fosinopril/hydrochlorothiazide	10/12.5, 20/12.5
	Quinapril/hydrochlorothiazide	10/12.5, 20/12.5, 20/25
	Benazepril/hydrochlorothiazide	5/6.25, 10/12.5, 20/12.5, 20/25
	Moexipril/hydrochlorothiazide	7.5/12.5, 15/25
Angiotensin II receptor blocker/diuretic	Losartan/hydrochlorothiazide	50/12.5, 100/25
	Valsartan/hydrochlorothiazide	80/12.5, 160/12.5
	Irbesartan/hydrochlorothiazide	75/12.5, 150/12.5, 300/12.5
	Candesartan/hydrochlorothiazide	16/12.5, 32/12.5
	Telmisartan/hydrochlorothiazide	40/12.5, 80/12.5
Ca channel blocker/ACE inhibitor	Amlodipine/benazepril	2.5/10, 5/10, 5/20, 10/20
	Verapamil (extended-release)/trandolapril	180/2, 240/1, 240/2, 240/4
	Felodipine (extended-release)/enalapril	5/5
Vasodilator/diuretic	Hydralazine/hydrochlorothiazide	25/25, 50/25, 100/25
	Prazosin/polythiazide	1/0.5, 2/0.5, 5/0.5
Triple combination	Reserpine/hydralazine/hydrochlorothiazide	0.10/25/15

Achieving adequate control often requires several evaluations and changes in drug therapy. Reluctance to titrate or add drugs until BP is at an acceptable level must be overcome. Lack of patient adherence, particularly because lifelong treatment is required, can interfere with adequate BP control. Education, with empathy and support, is essential for success.

Drugs for Hypertension

Diuretics: Main classes (see Table 5: [Arterial Hypertension: Oral Diuretics for Hypertension](#)) are thiazide-type diuretics, loop diuretics, and K-sparing diuretics. Loop diuretics are used to treat hypertension only in patients who have lost > 50% of kidney function; these diuretics are given twice/day. Diuretics modestly reduce plasma volume and reduce vascular resistance, possibly via shifts in Na from intracellular to extracellular loci. These drugs are the least expensive initial therapy, and the dose needed is small, especially for the elderly (eg, for most people > 60 hydrochlorothiazide 12.5 mg is sufficient). Thiazide-type diuretics are most commonly used. In addition to other antihypertensive effects, they cause vasodilation as long as intravascular volume is normal. All thiazides are equally effective in equivalent doses.

All diuretics except the K-sparing distal tubular diuretics cause significant K loss, so serum K is measured q 1 mo until the level stabilizes. Unless serum K is normalized, K channels in

the arterial walls close and the resulting vasoconstriction makes achieving the BP goal difficult. Patients with K levels < 3.5 mEq/L are given K supplements. Supplements may be continued long-term at a lower dose, or a K-sparing diuretic (eg, daily [spironolactone](#) 25 to 100 mg, [triamterene](#) 50 to 150 mg, [amiloride](#) 5 to 10 mg) may be added.

Supplements or addition of a K-sparing diuretic is also recommended for any patients who are also taking digitalis, have a known heart disorder, have an abnormal ECG, have ectopy or arrhythmias, or develop ectopy or arrhythmias while taking a diuretic. Although the K-sparing diuretics do not cause hypokalemia, hyperuricemia, or hyperglycemia, they are not as effective as thiazide-type diuretics in controlling hypertension and thus are not used for initial treatment. K-sparing diuretics or supplements are not needed when an ACE inhibitor or angiotensin II receptor blocker is used because these drugs increase serum K.

In most patients with diabetes, thiazide-type diuretics do not affect control of diabetes. Uncommonly, diuretics precipitate or worsen type 2 diabetes in patients with metabolic syndrome.

Thiazide-type diuretics can increase serum cholesterol slightly (mostly low density lipoprotein) and also increase triglyceride levels, although these effects may not persist > 1 yr. Furthermore, levels seem to increase only in a few patients. The increase is apparent within 4 wk of treatment and can be ameliorated by a low-fat diet. The possibility of a slight increase in lipid levels does not contraindicate diuretics in hyperlipidemic patients.

A hereditary predisposition probably explains the few cases of gout due to diuretic-induced hyperuricemia. Diuretic-induced hyperuricemia without gout does not require treatment or discontinuation of the diuretic.

Table 5

Oral Diuretics for Hypertension

Drug	Usual Dose* (mg)	Selected Adverse Effects
Thiazide type diuretics		
Bendroflumethiazide	2.5–5 once/day (maximum: 20)	Hypokalemia (which increases digitalis toxicity), hyperuricemia, glucose intolerance, hypercholesterolemia, hypertriglyceridemia, hypercalcemia, sexual dysfunction in men, weakness, rash; possibly increased blood levels of lithium
Chlorothiazide	62.5–500 bid (maximum: 1000)	
Chlorthalidone	12.5–50 once/day	
Hydrochlorothiazide	12.5–50 once/day	
Hydroflumethiazide	12.5–50 once/day	
Indapamide	1.25–5 once/day	
Methyclothiazide	2.5–5 once/day	
Metolazone (immediate-release)	0.5–1 once/day	
Metolazone (extended-release)	2.5–5 once/day	
K-sparing diuretics		
Amiloride	5–20 once/day	Hyperkalemia (particularly in patients with renal failure and in patients treated with an ACE inhibitor, angiotensin II receptor blocker, or NSAID), nausea, GI distress, gynecomastia, menstrual irregularities (with spironolactone); possibly increased blood levels of lithium
Eplerenone †	25–100 once/day	
Spironolactone †	25–100 once/day	
Triamterene	25–100 once/day	
*Larger doses may be required in patients with renal failure.		
†Aldosterone receptor blockers.		

β -Blockers: These drugs (see Table 6: [Arterial Hypertension: \$\beta\$ -Blockers for Hypertension](#)) slow heart rate and reduce myocardial contractility, thus reducing BP. All β -blockers are

similar in antihypertensive efficacy. In patients with diabetes, chronic peripheral arterial disease, or COPD, a cardioselective β -blocker ([acebutolol](#) , [atenolol](#) , [betaxolol](#) , [bisoprolol](#) , [metoprolol](#)) may be preferable, although cardioselectivity is only relative and decreases as dose increases. Even cardioselective β -blockers are contraindicated by asthma or by COPD with a prominent bronchospastic component.

β -Blockers are particularly useful in patients who have angina, who have had an MI, or who have HF. These drugs are no longer considered problematic for the elderly.

β -Blockers with intrinsic sympathomimetic activity (eg, [acebutolol](#) , [carteolol](#) , [penbutolol](#) , [pindolol](#)) do not adversely affect serum lipids; they are less likely to produce severe bradycardia.

β -Blockers have CNS adverse effects (sleep disturbances, fatigue, lethargy) and exacerbate depression. [Nadolol](#) affects the CNS the least and may be best when CNS effects must be avoided. β -Blockers are contraindicated in patients with 2nd- or 3rd-degree atrioventricular block, asthma, or sick sinus syndrome.

Ca channel blockers: Dihydropyridines (see Table 7: [Arterial Hypertension: Calcium Channel Blockers for Hypertension](#) ) are potent peripheral vasodilators and reduce BP by decreasing TPR; they sometimes cause reflexive tachycardia. The nondihydropyridines [verapamil](#) and [diltiazem](#) slow the heart rate, decrease atrioventricular conduction, and decrease myocardial contractility. These drugs should not be prescribed for patients with 2nd- or 3rd-degree atrioventricular block or with left ventricular failure.

Long-acting [nifedipine](#) , [verapamil](#) , or [diltiazem](#) is used to treat hypertension, but short-acting [nifedipine](#) and [diltiazem](#) are associated with a high rate of MI and are not recommended.

A Ca channel blocker is preferred to a β -blocker in patients with angina pectoris and a bronchospastic disorder, with coronary spasms, or with Raynaud's disease.

ACE inhibitors: These drugs (see Table 8: [Arterial Hypertension: ACE Inhibitors and Angiotensin II Receptor Blockers for Hypertension](#) ) reduce BP by interfering with the conversion of angiotensin I to angiotensin II and by inhibiting the degradation of bradykinin, thereby decreasing peripheral vascular resistance without causing reflex tachycardia. These drugs reduce BP in many hypertensive patients, regardless of plasma renin activity. Because these drugs provide renal protection, they are the drugs of choice for diabetics and may be preferred for blacks.

A dry, irritating cough is the most common adverse effect, but angioedema is the most serious and, if it affects the oropharynx, can be fatal. Angioedema is most common among blacks and smokers. ACE inhibitors may increase serum K and creatinine levels, especially in patients with chronic renal failure and those taking K-sparing diuretics, K supplements, or NSAIDs. ACE inhibitors are the least likely of the antihypertensives to cause erectile dysfunction. ACE inhibitors are contraindicated during pregnancy. In patients with a renal disorder, serum creatinine and K levels are monitored at least q 3 mo. Patients who have stage 3 nephropathy (estimated GFR of < 60 mL/min to > 30 mL/min) and are

Table 6

 [β-Blockers for Hypertension](#)

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Table 7

 [Calcium Channel Blockers for Hypertension](#)

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Table 8

 [ACE Inhibitors and Angiotensin II Receptor Blockers for Hypertension](#)

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given ACE inhibitors can usually tolerate up to a 30 to 35% increase in serum creatinine above baseline. ACE inhibitors can cause acute renal failure in patients who are hypovolemic or who have severe HF, severe bilateral renal artery stenosis, or severe stenosis in the artery to a solitary kidney.

Thiazide-type diuretics enhance the antihypertensive activity of ACE inhibitors more than that of other classes of antihypertensives.

Angiotensin II receptor blockers: These drugs (see Table 8: [Arterial Hypertension: ACE Inhibitors and Angiotensin II Receptor Blockers for Hypertension](#)) block angiotensin II receptors and therefore interfere with the renin-angiotensin system. Angiotensin II receptor blockers and ACE inhibitors are equally effective as antihypertensives. Angiotensin II receptor blockers may provide added benefits via tissue ACE blockade. The 2 classes have the same beneficial effects in patients with left ventricular failure or with nephropathy due to type 1 diabetes. An angiotensin II receptor blocker used with an ACE inhibitor or a β -blocker reduces the hospitalization rate for patients with HF. Angiotensin II receptor blockers may be safely started in people < 60 with initial serum creatinine of ≤ 3 mg/dL.

Incidence of adverse events is low; angioedema occurs but much less frequently than with ACE inhibitors. Precautions for use of angiotensin II receptor blockers in patients with renovascular hypertension, hypovolemia, and severe HF are the same as those for ACE inhibitors. Angiotensin II receptor blockers are contraindicated during pregnancy.

Direct renin inhibitors: [Aliskiren](#), a direct renin inhibitor, is used in the management of hypertension. Dosage is 150 to 300 mg po once/day, with a starting dose of 150 mg. Clinical trials are ongoing to assess its efficacy for slowing diabetic nephropathy and reducing mortality in HF.

Adrenergic modifiers: This class (see Table 9: [Arterial Hypertension: Adrenergic Modifiers for Hypertension](#)) includes central α_2 -agonists, postsynaptic α_1 -blockers, and peripheral-acting adrenergic blockers.

α_2 -Agonists (eg, [methyldopa](#), [clonidine](#), [guanabenz](#), [guanfacine](#)) stimulate α_2 -adrenergic receptors in the brain stem and reduce sympathetic nervous activity, lowering BP. Because they have a central action, they are more likely than other antihypertensives to produce drowsiness, lethargy, and depression; they are no longer widely used. [Clonidine](#) can be applied transdermally once/wk as a patch; thus, it may be useful for nonadherent patients (eg, those with dementia).

Postsynaptic α_1 -blockers (eg, [prazosin](#), [terazosin](#), [doxazosin](#)) are no longer used for primary treatment of hypertension because evidence suggests no reduction in mortality. Also, [doxazosin](#) used alone or with antihypertensives other than diuretics increases risk of HF.

Peripheral-acting adrenergic blockers (eg, [reserpine](#), guanethidine, guanadrel) deplete tissue stores of norepinephrine. [Reserpine](#) also depletes the brain of norepinephrine and serotonin. Guanethidine and guanadrel block sympathetic transmission at the neuroeffector junction. Guanethidine, in particular, is potent but difficult to titrate, so it is rarely used. Guanadrel is shorter acting and has fewer adverse effects. These 3 adrenergic blockers are not routinely recommended for initial therapy; they are used as 3rd or 4th drugs if required.

Direct vasodilators: These drugs (including [minoxidil](#) and [hydralazine](#)—see Table 10: [Arterial Hypertension: Direct Vasodilators for Hypertension](#)) work directly on vessels, independently of the autonomic nervous system. [Minoxidil](#) is more potent than [hydralazine](#) but has more adverse effects, including Na and water retention and

Table 9

[Adrenergic Modifiers for Hypertension](#)

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hypertrichosis, which is poorly tolerated by women. [Minoxidil](#) should be reserved for severe, refractory hypertension. [Hydralazine](#) is used during pregnancy (eg, for preeclampsia) and as an adjunct antihypertensive. Long-term, high-dose (> 300 mg/day) [hydralazine](#) has been associated with a drug-induced lupus syndrome, which resolves when the drug is stopped.

Table 10

Direct Vasodilators for Hypertension

Drug	Usual Dose (mg)	Selected Adverse Effects*	Comments
Hydralazine	10 – 50 qid	Positive antinuclear antibody test, drug-induced lupus (rare at recommended doses)	Augments vasodilating effects of other vasodilating drugs
Minoxidil	1.25 – 40 bid	Na and water retention, hypertrichosis; possibly new or worsening pleural and pericardial effusions	Reserved for severe, refractory hypertension

*Both drugs may cause headache, tachycardia, and fluid retention and may precipitate angina in patients with coronary artery disease.

Last full review/revision July 2007 by George L. Bakris, MD
Content last modified July 2007

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