CONT. hypovolemia and responds to correction of the volume deficit with isotonic saline.

The most common conditions that cause metabolic alkalosis are associated with chloride depletion (vomiting, nasogastric suction, and diuretic use). Although upper GI disorders (such as vomiting) are the most common GI source for the generation of metabolic alkalosis, rare lower GI disorders that cause chloride depletion include forms of chloride-secretory diarrhea such as villous adenoma and congenital chloridorrhea that lead to an increase in bicarbonate retention. A "contraction alkalosis" results from loss of extracellular fluid containing low amounts of bicarbonate that contract the extracellular volume around a constant amount of existing circulating bicarbonate.

In patients with low urine chloride (<15 mEq/L [15 mmol/L]), normal/low intravascular volume, and normal/low extracellular volume, treatment consists of administration of saline together with repletion of potassium (saline-responsive metabolic alkalosis) while addressing the primary cause of the alkalosis. In contrast, those with a low urine chloride (<15 mEq/L [15 mmol/L]) and normal/low intravascular volume but with an increased extravascular volume have a disorder of effective arterial blood volume such as heart failure, cirrhosis, or hypoalbuminemia from the nephrotic syndrome that results in secondary hyperaldosteronism, sodium and bicarbonate retention, and an increase in extracellular volume manifested by edema. Treatment is tailored to improving effective arterial blood volume and diuresis. For those who have a high urine chloride (>15 mEq/L [15 mmol/L]) with elevated blood pressure, hypokalemia, and do not appear to be overtly volume overloaded, a mineralocorticoid excess disorder must be considered (saline-resistant metabolic alkalosis). The lack of an overt increase in extravascular volume in the latter condition is often described as "aldosterone escape," in which sodium balance is attained through spontaneous diuresis that occurs after initial sodium retention that returns the vascular volume toward normal. This condition is treated with potassium repletion and treatment of the underlying condition.

Rarely, patients with metabolic alkalosis may appear to have clinical features consistent with saline-responsive metabolic alkalosis (normal/low extracellular fluid status, normal/low blood pressure) but have a urine chloride of >15 mEq/L (15 mmol/L). Diuretic use and inherited kidney disorders of sodium and chloride handling such as Bartter and Gitelman syndromes can mimic this presentation. These are two autosomal recessive genetic disorders of renal sodium and chloride transporters that clinically mimic loop diuretic and thiazide diuretic use, respectively. These diagnoses should be considered only after urine diuretic screening. Treatment focuses on the correction of volume and potassium depletion, and, in the case of Bartter syndrome, inhibition of prostaglandin production with indomethacin or ibuprofen to reduce sodium and chloride delivery to the distal tubule.

KEY POINTS

- The assessment of blood pressure and volume status is critical to identify the likely etiology of metabolic alkalosis.
- Treatment of metabolic alkalosis is based upon urine chloride and both extracellular and intravascular volume assessment.

Respiratory Acidosis

Respiratory acidosis is the result of inadequate CO_2 exchange from the pulmonary capillaries to the alveoli; the resultant arterial CO_2 retention (hypercapnia) is initially buffered by water, leading to formation of excess hydrogen ions and bicarbonate. Thus, the typical arterial blood gas in this setting demonstrates an elevation in P_{CO_2}, a decrease in pH, and a slight increase in bicarbonate (see Table 12).

The most common causes of respiratory acidosis are inadequate ventilation, interference with arterial-alveolar gas exchange, and airway obstruction (**Table 18**).

Clinical manifestations of respiratory acidosis are difficult to ascribe specifically to hypercapnia itself given the associated hypoxemia. Neurologic symptoms include headache, anxiety,

TABLE 18. Causes of Respiratory Acidosis

Inadequate Ventilation
Decreased respiratory drive: head trauma; cerebrovascular accident; obesity-hypoventilation syndrome; central sleep apnea; CNS tumor; edema; infection; medications (anesthetics, sedatives, opiates)
Neuromuscular dysfunction: spinal cord injury; Guillain-Barré syndrome; amyotrophic lateral sclerosis; periodic paralysis
Musculoskeletal dysfunction: kyphoscoliosis; severe obesity; polymyositis; severe hypokalemia or hypophosphatemia
Impaired Arterial-Alveolar Gas Exchange
Pneumonia
Acute lung injury/acute respiratory distress syndrome
Cardiogenic pulmonary edema
Pneumothorax
Hemothorax
Emphysema
Interstitial lung disease
Pulmonary fibrosis
Pulmonary embolism
Airway Obstruction
Upper airway: tonsillar hypertrophy; vocal cord paralysis; foreign body aspiration; laryngospasm; tracheal stenosis; angioedema
Lower airway: status asthmaticus; COPD

CNS = central nervous system.

CONT. blurred vision, and tremor. When severe, symptoms can progress to confusion, somnolence, or seizures. Chronic respiratory acidosis may have milder neurologic effects such as memory loss, inattentiveness, or irritability. Additional symptoms of respiratory acidosis include cardiovascular effects such as vasodilation and tachycardia that may evolve to cardiac arrhythmias and decreased cardiac output. When respiratory acidosis is severe, renal vasoconstriction with enhanced sodium retention occurs, typically seen in those with severe lung disease and cor pulmonale.

Treatment entails oxygen supplementation and mechanical ventilation to decrease CO_2 if necessary while treating the underlying disease.

KEY POINT

- Respiratory acidosis is associated with hypercapnia, with an elevation in P_{CO_2}, a decrease in pH, and a slight increase in bicarbonate.

Respiratory Alkalosis

Respiratory alkalosis is the result of enhanced CO_2 exchange from the pulmonary capillaries to the alveoli and to the expired air. Without compensatory mechanisms, the fall in arterial CO_2 (hypocapnia) leads to a rapid increase in arterial pH. However, immediate diffusion of hydrogen ions from intracellular stores (from hemoglobulin, phosphate, and other protein buffers) binds with bicarbonate, causing a reduction in serum bicarbonate, thus limiting this consequence. The typical arterial blood gas in this setting demonstrates a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate (see Table 12). Other electrolyte abnormalities may result from respiratory alkalosis, including an increase in cellular lactic acid production, an increase in the anion gap in part from an increase in negatively charged albumin, and a decrease in ionized calcium from enhanced binding to negatively charged albumin. Finally, severe hypophosphatemia can occur due to a shift of phosphate from extracellular to intracellular fluid.

The most common causes of respiratory alkalosis are an enhanced respiratory drive, hypoxemia, and pulmonary disease with stimulation of thoracic stretch receptors (**Table 19**). Symptoms include tachypnea and related neurologic findings such as lightheadedness, numbness and paresthesias, cramps, confusion, and, rarely, seizures. An important consideration when evaluating a patient with respiratory alkalosis is the potential for salicylate intoxication, which in its early phases presents with mental status changes, respiratory alkalosis, and an anion gap metabolic acidosis.

Treatment of respiratory alkalosis is directed at correction of the primary disorder. For salicylate intoxication, forced diuresis, urine alkalinization, or hemodialysis should be considered. For anxiety-induced or psychogenic hyperventilation, increasing the inspired P_{CO_2} by closed bag rebreathing may increase the P_{CO_2} and improve

TABLE 19. Causes of Respiratory Alkalosis

Enhanced Respiratory Drive
Sepsis
Hepatic failure
Anxiety
Psychosis
Subarachnoid hemorrhage
Pregnancy
Nicotine
Medications: salicylates; theophylline/aminophylline
Hormones: progesterone; medroxyprogesterone; epinephrine; norepinephrine; angiotensin II
Hypoxemia
High altitude
Severe anemia
Hypotension
Chronic heart failure
Pulmonary parenchymal disease
Pulmonary Disease with Thoracic Stretch Receptor Stimulation
Pneumonia
Acute respiratory distress syndrome
Pulmonary embolism
Hemothorax
Pneumothorax
Pulmonary edema

symptoms. In rare circumstances when there is severe alkalemia (for example, pH >7.55) with hemodynamic instability, arrhythmias, or altered mental status, strategies to reduce bicarbonate via acetazolamide or controlled hypoventilation with mechanical ventilation to increase P_{CO_2} may be considered.

KEY POINT

- Respiratory alkalosis is associated with hypocapnia, with a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate.

Hypertension

Epidemiology

Hypertension prevalence in the United States is increasing, albeit more slowly over the past decade, and is estimated to be 29%. Efforts to effectively treat hypertension have slightly improved over time, but only approximately 50% of patients with hypertension are controlled to a blood pressure goal of <140/90 mm Hg.

Consequences of Sustained Hypertension

End-Organ Injury

In the brain and central nervous system, elevated blood pressure can lead to cerebral aneurysms, which may rupture (subarachnoid hemorrhage), and retinal hemorrhage. Long-standing hypertension can lead to arteriolosclerosis, resulting in arteriolar narrowing and distal ischemia. Clinical consequences include lacunar infarction and dementia.

In the heart, increased blood pressure leads to a compensatory myocardial hypertrophy that results in impaired relaxation (diastolic dysfunction) over time, which ultimately can lead to heart failure.

In the medium to large blood vessels, hypertension may cause pressure-related injury (aortic aneurysms and dissection) and contribute to the development of atherosclerosis through disruption of the vascular endothelium. When combined with elevated cholesterol, diabetes mellitus, and proinflammatory cytokines, this results in plaque formation. Plaque formation may result in thrombotic and embolic complications such as myocardial infarction, renal artery stenosis, embolic stroke, and atheroembolic peripheral arterial disease.

In the kidneys, hypertension has adverse effects on the renal vasculature, which may ultimately lead to kidney dysfunction. Chronic hypertension is associated with the development of both arteriolosclerosis and atherosclerosis. With severe hypertension, arteriolar injury with proliferation ("onion skin" lesions) and fibrinoid necrosis can occur, clinically manifesting as acute kidney injury with features of thrombotic microangiopathy and hematuria. Although debate exists as to whether hypertension as an isolated condition causes end-stage kidney disease, it clearly contributes to an accelerated progression to kidney failure in susceptible persons.

Clinical Impact

Hypertension is considered a primary cardiovascular risk factor that contributes to the development of stroke, coronary heart disease, peripheral vascular disease, and heart failure. In particular, hypertension is the strongest risk factor for hemorrhagic and ischemic stroke. Epidemiologic studies indicate that systolic blood pressures >115 mm Hg and diastolic blood pressures >75 mm Hg are associated in a linear fashion with cardiovascular events (**Figure 9**). Nearly 54% of stroke events and 47% of ischemic heart disease worldwide can be attributable

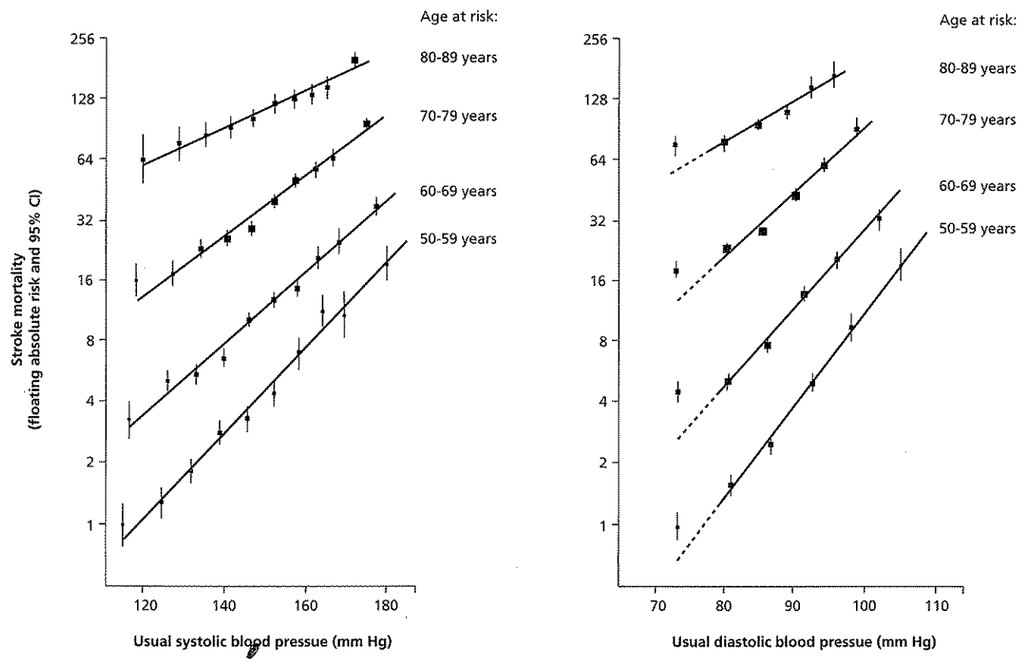

FIGURE 9. Stroke mortality rate by systolic and diastolic blood pressure, stratified by age. Meta-analysis of 61 prospective observational studies in adults with no previous vascular disease. "Usual" is defined as the long-term average blood pressure, accounting for blood pressure as a time-dependent variable in the studies included for meta-analysis.

Reprinted from The Lancet. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. 2002 Dec 14;360(9349):1903-13. [PMID: 12493255] Copyright 2002, with permission from Elsevier.

to high blood pressure, which equates to 7.6 million premature deaths (13.5% of total) and 92 million disability-adjusted life years (6% of total). Despite these epidemiologic studies, treatment of hypertension to 115/75 mm Hg has not been demonstrated to correlate with equivalent reductions in cardiovascular risk.

KEY POINTS

- Only approximately 50% of patients with hypertension are controlled to a blood pressure goal of <140/90 mm Hg.
- Nearly 54% of stroke events and 47% of ischemic heart disease worldwide can be attributable to high blood pressure, which equates to 7.6 million premature deaths (13.5% of total) and 92 million disability-adjusted life years (6% of total).

Blood Pressure Measurement

Proper Technique

The current standard of care for blood pressure measurement employs the oscillometric method using either a properly calibrated automated device or manual measurement. This can be performed in the office or home, but the technique follows the same guidelines:

- a quiet environment with the patient in a seated position, with the back supported and feet on the floor following 5 minutes of rest
- the arm supported with the cuff at heart level; measurement should not be taken through clothes
- the cuff is placed on the upper arm, and the bladder portion should be large enough to encircle at least 80% of the arm to ensure that there is uniform compression of the brachial artery; proper cuff size is estimated by aligning the cuff parallel to the arm and wrapping the arm with the bladder; the bladder width should be large enough to encircle half the upper arm; the cuff should be inflated to a high enough pressure to exclude an auscultatory gap
- at least two measurements should be taken at least 30 seconds apart on each assessment, with repeated measurements as needed until two values are within 5 mm Hg of each other

Manual (Auscultatory) Blood Pressure Monitoring

The manual method for measuring blood pressure involves a cuff-based sphygmomanometer and stethoscope. The blood pressure is measured with the lower end of the cuff 2 to 3 cm above the antecubital fossa and the stethoscope over the brachial artery in the antecubital fossa. The cuff should be inflated at least 30 mm Hg above the estimated systolic blood pressure (indicated by disappearance of the palpated brachial pulse) to avoid error in blood pressure measurement by misinterpreting the auscultatory gap.

Electronic Blood Pressure Monitoring

Electronic blood pressure monitors are now extremely common in the office setting as well as at home due to the convenience and the relative standardization of measurement (through the elimination of user variation/error). These devices measure blood pressure through similar oscillometric methodology as manual blood pressure cuff assessment. Sensors detect the disappearance of the brachial pulse upon inflation and the increasing amplitude of the pulse upon deflation. In general, the systolic blood pressure is slightly lower and the diastolic blood pressure slightly higher than an intra-arterial measurement. Electronic devices should be properly calibrated and inspected, and patients should be encouraged to bring their devices to the office to compare readings obtained on personal versus office devices.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) uses a continuously worn device that can be programmed to measure blood pressure every 15 to 20 minutes during the day and every 30 to 60 minutes at night. ABPM-ascertained hypertension is associated with a higher risk of cardiovascular death compared with hypertension determined in the office or at home (**Figure 10**). There is evidence supporting use of ABPM to confirm office-based blood pressure screening results to avoid misdiagnosis and overtreatment of individuals who may have elevated blood pressure readings only in the clinic. Beyond the benefits of accurate diagnosis of hypertension, there are numerous clinical circumstances under which ABPM provides valuable additional information over office-based measurements, including the evaluation of white coat hypertension, apparent resistant hypertension, masked hypertension, and suspected episodic hypertension.

Normal ranges for ABPM depend on the time frame of monitoring. Normal average daytime blood pressure by ABPM should be <140/90 mm Hg, with a normal nighttime average blood pressure of <125/75 mm Hg; the overall 24-hour average blood pressure should be <135/85 mm Hg. ABPM also can be used to determine if dipping is present, which is defined as the normal decrease in blood pressure at night by approximately 15% compared with daytime values. Failure of nighttime dipping is associated with an increased incidence of left ventricular hypertrophy. Additionally, elevated nighttime blood pressure by ABPM is strongly associated with an increased risk of cardiovascular death (see Figure 10).

Home Blood Pressure Monitoring

Patients can be instructed to perform frequent home blood pressure measurements, with readings at various times during the day totaling at least 12 measurements over 1 week. For a given systolic or diastolic blood pressure value, a home blood pressure average is associated with a risk of cardiovascular death higher than an office-based reading but lower than an ABPM average (see Figure 10). Home blood pressure monitoring

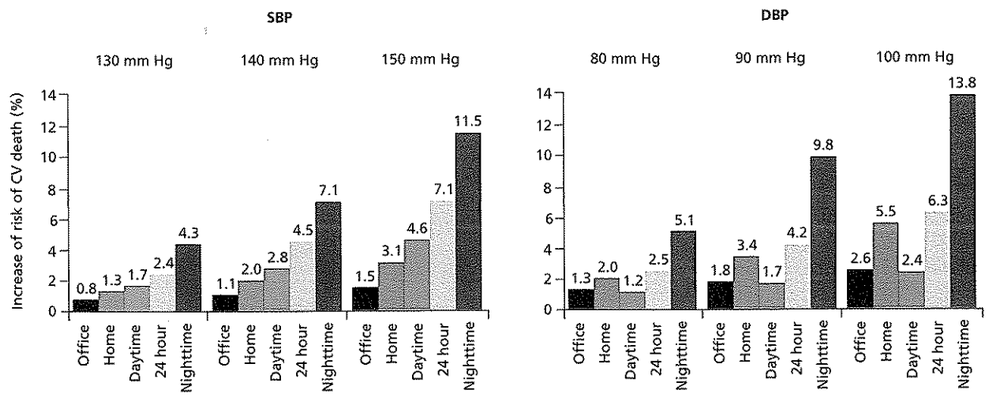

FIGURE 10. Increase in 11-year risk of cardiovascular mortality for 10 mm Hg increase in office, home, and ambulatory blood pressure at various initial blood pressure values. There were 2051 subjects. Office blood pressure at initial visit and after ambulatory blood pressure were averaged and pooled, two home blood pressure measurements (7 AM and 7 PM) concurrent with ambulatory blood pressure on the contralateral arm were averaged, and ambulatory blood pressure values were averaged over 24 hours, day (7 AM-11 PM), and night (11 PM-7 AM). CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure.

is beneficial in monitoring blood pressure response to treatment, including lifestyle modifications. Patients should be instructed on appropriate technique and counseled on the frequency and timing of measurements to avoid very frequent blood pressure monitoring and the potential for medication self-adjustment. Whenever possible, upper-arm cuffs should be used unless medical conditions (such as trauma or surgery to the upper arm) require alternative sites; in these circumstances, wrist measurements are an alternative. Systolic pressure is higher and diastolic pressure is lower in the distal arteries, and calibration is critical in interpreting these values. Finger measurements lack accuracy and validation and thus should be discouraged.

KEY POINT

- Hypertension ascertained by ambulatory blood pressure monitoring is associated with a higher risk of cardiovascular death compared with hypertension determined in the office or at home.

Evaluation of the Patient with Newly Diagnosed Hypertension

The assessment of hypertension begins with proper determination of blood pressure, followed by evaluation of the patient's history, physical examination, screening laboratory data with a focus on the identification of specific causes (secondary hypertension), additional cardiovascular risk factors, and potential end-organ targets.

For the initial diagnosis of hypertension, most guidelines define hypertension as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg for office blood pressure readings (**Table 20**); however, exceptions exist for some subgroups, and guidelines continue to evolve. Importantly, a diagnosis should not be made in the office setting until the threshold blood pressure has been documented on at least three visits over a period of at least 1 week or longer. There is evidence that confirming clinic-based blood pressure elevations with ABPM is effective at avoiding overdiagnosis and overtreatment for patients in whom elevated blood pressures are detected only in the clinic.

TABLE 20. Classification of Blood Pressure for Adults

BP Category	Office-Based Readings (mm Hg)	24-Hour Ambulatory Readings (mm Hg)	Self-Recorded BP (mm Hg)
Normal	SBP <120 and DBP <80	<130/80	<135/85
Prehypertension	SBP 120-139 or DBP 80-89	—	—
Hypertension, Stage 1	SBP 140-159 or DBP 90-99	≥135/85	≥135/85
Hypertension, Stage 2	SBP ≥160 or DBP ≥100	—	—
White Coat Hypertension	≥140/90	<135/85	<135/85
Masked Hypertension	<140/90	>135/85	>135/85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

History

The history of a patient with newly diagnosed hypertension should consider the potential for a familial pattern of hypertension as well as a family history of heart disease, kidney disease, and stroke. Questions should also focus on related symptoms, including episodic (such as headache or palpitations) and persistent (such as vision changes or foamy urine) symptoms, as well as risk factors for hypertension and cardiovascular disease (obesity, smoking, alcohol, caffeine, diet, diabetes, emotional stress, sleep apnea). A review of medications, including over-the-counter and herbal medications, is important because a number of these agents can contribute to elevated blood pressure (**Table 21**).

Physical Examination

The physical examination of a patient with newly diagnosed hypertension should focus on the following:

- accurate blood pressure measurement in both arms
- potential causes of hypertension such as the presence of an abdominal bruit suggestive of renovascular hypertension or an enlarged/palpable thyroid suggestive of hyperthyroidism
- potential end-organ targets, including an eye examination to assess for arteriovenous nicking and papilledema as well as a cardiovascular examination to assess for volume status, pulses in all extremities, bruits, and left ventricular hypertrophy (left ventricular heave, S_4 gallop)

Testing

A patient with newly diagnosed hypertension should undergo laboratory testing for kidney function, fasting plasma glucose, fasting serum lipid panel, serum potassium, and serum calcium. Electrocardiography (ECG) should be obtained to assess for the presence of left ventricular hypertrophy (LVH) or silent myocardial injury. Although echocardiography is a more sensitive test for LVH, in general, echocardiography is not indicated in the assessment of hypertension except in patients with known heart disease; the presence of left bundle branch block on ECG, given its association with sudden death; or suspected white coat hypertension.

A urinalysis should be performed to assess for albuminuria and hematuria. Standard urine dipsticks do not detect moderately increased albuminuria (formerly known as microalbuminuria), which is an increasingly recognized marker of microvascular injury and is independently associated with an increased risk of cardiovascular events in hypertensive individuals with or without diabetes. Albumin generally comprises approximately 50% of the total protein excreted in the urine, with the remainder comprised of proteins of smaller molecular weight that are secreted into the urine. Because albuminuria, and not total proteinuria, has been associated with cardiovascular events, testing should be directed in this fashion. Measurement of a first morning urine sample for albumin and creatinine can permit calculation of an albumin-creatinine ratio, which is a good estimate for moderately increased albuminuria (30-300 mg/g).

The use of plasma renin activity to risk-stratify patients with hypertension or to predict response to specific interventions is of unclear value and is not recommended for routine use.

TABLE 21. Over-the-Counter and Prescription Agents that Increase Blood Pressure

Type	Agent	Mechanism(s)
OTC	Black licorice (European)	Mineralocorticoid activity enhancement; sodium retention
OTC	Ethanol	Adrenergic stimulation
OTC	NSAIDs	Sodium retention
OTC/Rx	Sympathomimetics; appetite suppressants; decongestants; vigilance enhancers (e.g., amphetamines)	Vasoconstriction; sodium retention
Rx	Selective serotonin or serotonin-norepinephrine reuptake inhibitors	Adrenergic stimulation
Rx	Erythrocyte stimulation agents (e.g., erythropoietins)	Vasoconstriction
Rx	Antiretroviral therapies	Not clear
Rx	Vascular endothelial growth factor antagonists (e.g., bevacizumab)	Vasoconstriction (endothelial dysfunction)
Rx	Glucocorticoids (e.g., prednisone)	Sodium retention; weight gain
Rx	Oral contraceptives	Increased renin-angiotensin system activity; sodium retention
—	Caffeine	Adrenergic stimulation
—	Cocaine; 3,4-methylenedioxymethamphetamine (also known as ecstasy); recreational drugs	Adrenergic stimulation

OTC = over the counter; Rx = prescription.

However, there are circumstances in which the plasma aldosterone-plasma renin ratio may be used to screen for primary hyperaldosteronism. The 2008 Endocrine Society recommendations include screening patients with hypokalemia and hypertension as well as patients with moderate to severe hypertension even without significant hypokalemia (>160/100 mm Hg) and those with resistant hypertension. See Hypokalemia and Hypertension for more information.

KEY POINTS

HVC
- Echocardiography is not routinely indicated in the assessment of hypertension except in patients with known heart disease; the presence of left bundle branch block on electrocardiogram, given its association with sudden death; or suspected white coat hypertension.
- Plasma aldosterone-plasma renin ratio determination is recommended for patients with hypokalemia and hypertension as well as patients with moderate to severe hypertension even without significant hypokalemia and those with resistant hypertension.

Classification of Hypertension

Overview

The eighth report of the Joint National Committee (JNC 8), along with the European Society of Hypertension and the Canadian Hypertension Education Program, all currently define hypertension for non-elderly patients without chronic kidney disease (CKD) or diabetes as ≥140/90 mm Hg.

Prehypertension

JNC 8 did not address the concept of prehypertension. However, JNC 7 defined prehypertension as a systolic blood pressure of 120-139 mm Hg or a diastolic blood pressure of 80-89 mm Hg. This definition arose from the epidemiologic associations of "high normal" blood pressure and increased cardiovascular risk (see Figure 9), and the observed progression of many to overt hypertension. It is reasonable to identify and educate persons with prehypertension regarding their risk; however, data supporting the use of pharmacologic treatment to prevent complications or progression are lacking. Thus, treatment should focus on lifestyle modification and close monitoring, described later.

Stage 1 and 2 Hypertension

Hypertension is often classified by severity to bring awareness to the strong relationship of increasing blood pressure and cardiovascular morbidity and mortality (see Figure 9). The JNC 7 defines stage 1 hypertension as a systolic blood pressure of 140-159 mm Hg or a diastolic blood pressure of 90-99 mm Hg; stage 2 hypertension is defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥100 mm Hg (see Table 20). These classifications have treatment implications, as those with stage 1 with average blood pressure values just above the defined threshold may be amenable to lifestyle modification with close monitoring, whereas those with stage 2 typically require combination therapy to achieve adequate blood pressure control. See Management for more information.

KEY POINTS

- Several guidelines define hypertension for non-elderly patients without chronic kidney disease or diabetes mellitus as ≥140/90 mm Hg.
- Treatment of prehypertension should focus on lifestyle modification and close monitoring.

Primary Hypertension

Pathogenesis

Approximately 90% of patients diagnosed with hypertension have primary hypertension (formerly known as essential hypertension), in which there is no identifiable anatomic or screening laboratory finding that provides insight as to the cause of hypertension. For most patients, the pathogenesis remains unclear. A number of potential mechanisms have been proposed, with experimental data supporting all of the following theories: abnormal sodium handling by the kidney, increased sympathetic tone, and increased activity of the renin-angiotensin-aldosterone axis.

Genetic Factors

Increasingly, genetic studies have identified gene mutations or polymorphisms that may explain up to 20% to 30% of cases of primary hypertension. The best described mutations are those directly affecting sodium channels of the distal renal tubule and collecting duct as well as those that lead to excess mineralocorticoid effect upon the distal tubule. These defects lead to excess sodium reabsorption and hypertension. Other genetic polymorphisms that may predispose to hypertension involve oxidative stress mechanisms, mediators of vascular smooth muscle tone, and vasoactive mediators.

Societal Factors

The increased prevalence of hypertension is a result of worldwide changes in diet and lifestyle over time. The adoption of a Western diet and an increase in sodium intake has resulted in prevalence rates of 20% to 30% in geographic regions that previously had virtually no prior prevalence of hypertension. Age, race, obesity, insulin resistance, and hyperuricemia have all emerged as significant risk factors for hypertension.

Management

General Approach

The JNC 8 hypertension management recommendations are summarized as follows:

- Lifestyle modifications: implement in all patients with prehypertension and hypertension. Continue even if pharmacologic treatment becomes necessary. Modifiable risk factors should be treated.
- General adult population <60 years of age: pharmacologic treatment is recommended if the systolic blood pressure is ≥140 mm Hg or the diastolic blood pressure is ≥90 mm Hg. The goal of therapy is <140/90 mm Hg.
- Patients ≥60 years of age: pharmacologic treatment is recommended if the systolic blood pressure is ≥150 mm Hg or the diastolic blood pressure is ≥90 mm Hg. The goal of therapy is <150/90 mm Hg, although patients with a blood pressure of <140/90 mm Hg on well-tolerated therapy do not need to have their treatment changed.
- Patients ≥18 years of age with diabetes or CKD: the initiation threshold and goal for pharmacologic treatment is 140/90 mm Hg.
- General non-black population, including those with diabetes: thiazide diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) all may be considered for initial treatment.
- Black patients, including those with diabetes: initial therapy should be a thiazide diuretic or CCB. As a group, black patients have less blood pressure reduction with equivalent ACE inhibitor dosing compared with non-black patients. Furthermore, black patients initially treated with ACE inhibitors rather than CCBs have about a 50% higher rate of stroke, and combined cardiovascular outcomes are better with a thiazide diuretic than with an ACE inhibitor.
- All patients (regardless of race or the presence/absence of diabetes) >18 years of age with CKD (including those with and those without proteinuria): initial therapy should be an ACE inhibitor or ARB because these agents are renoprotective and improve renal outcomes.
- Black patients with CKD but without proteinuria: the initial agent can be a CCB, thiazide diuretic, ACE inhibitor, or ARB. If the initial choice is not an ACE inhibitor or ARB, then one of these should be the second drug added if necessary to lower the blood pressure to target (<140/90 mm Hg).

Visit http://jama.jamanetwork.com/article.aspx?articleid=1791497 for more information on the JNC 8 recommendations.

Lifestyle Modifications

A critical component of blood pressure treatment is modification of diet and activity. Lifestyle interventions should be stressed to patients not only with sustained hypertension but also to those with prehypertension to reduce future hypertension and cardiovascular disease. Examples of nonpharmacologic measures include the following: 1) a low sodium diet; 2) a diet such as DASH (Dietary Approaches to Stop Hypertension) that emphasizes vegetables, fruits, whole grains, legumes, and low-fat dairy products and limits sweets, red meat, and saturated/total fat; 3) weight loss; and 4) exercise, which can be of significant benefit for blood pressure control and management.

All interventions produce a reduction in blood pressure, even in normotensive individuals, but their effects are magnified in those who are hypertensive. In adults up to age 75 to 80 years with a blood pressure of 120-159/80-95 mm Hg, reducing sodium intake from 3300 mg/d to 1500 mg/d lowers blood pressure by an average of 7/3 mm Hg. A more modest reduction of approximately 1150 mg/d reduces blood pressure by an average of 3 to 4/1 to 2 mm Hg. Combining a reduced sodium intake with a DASH dietary pattern has an additive effect on lowering blood pressure. Weight loss of 5.0 kg (11 lb) may be expected to lead to a reduction of 4/3 mm Hg, although this effect may be higher in those who are hypertensive. Independent of weight loss or dietary intervention, aerobic exercise for 40 minutes 3 to 4 times per week lowers blood pressure by 2 to 5/1 to 4 mm Hg. Thus, implementing lifestyle interventions can produce reductions in blood pressure equivalent to antihypertensive agents and should be recommended for all patients with hypertension. Other interventions such as moderating alcohol intake and increasing potassium and calcium in the diet have more modest and less reproducible effects in lowering blood pressure. Tobacco cessation strategies should be encouraged. Although tobacco use has variable effects upon blood pressure, the strong synergistic relationship between hypertension, tobacco use, and the development of atherosclerotic disease over time should be addressed at each visit.

Pharmacologic Therapy

In patients who are unresponsive to an adequate trial of lifestyle modification, pharmacologic therapy is indicated. Timing of initiation of medications should be dictated by the severity of hypertension. For example, a non-elderly patient with a systolic blood pressure of 140-150 mm Hg may benefit from a 3- to 6-month trial of lifestyle modification alone with close monitoring, whereas an individual with stage 2 hypertension or with evidence of end-organ disease should be started on medications together with lifestyle modification. The selection of initial antihypertensive therapy has been extensively reviewed for potential individual benefits in efficacy, overall mortality, cardiovascular-related mortality, and cardiovascular and renal events. In multiple reviews and meta-analyses, the attained blood pressure is far more critical than the agent used to achieve blood pressure control and prevent cardiovascular events. For this reason, the JNC 8 recommends the use of any one of four drug classes, thiazide diuretics (thiazides), CCBs, ACE inhibitors, and ARBs, as initial therapy in the general nonblack population (elderly and non-elderly). All performed similarly in preventing cardiovascular mortality and morbidity end points with the exception of heart failure, in which a slight advantage of thiazides over CCBs and ACE inhibitors and a slight advantage of ACE inhibitors over CCBs were noted in two trials. However, these differences were not considered by JNC 8 to be compelling.

In the general black population, initial therapy with a thiazide diuretic or CCB is recommended.

Specific non-recommended initial agents by JNC 8 include β-blockers (due to higher cardiovascular-related events and mortality compared with ARBs) and α-blockers (due to higher cardiovascular-related events and mortality compared with thiazides), although clinical conditions such as atrial fibrillation or benign prostatic hyperplasia may supersede these recommendations (**Table 22**).

See **Table 23** for a list of frequently used antihypertensive medications and their side effects.

Choice of Diuretic

Thiazide diuretics remain as a first-line option for the treatment of hypertension. Most large randomized clinical trials have been performed with either hydrochlorothiazide or chlorthalidone, medications with similar primary mechanism of action (inhibition of the Na^+Cl^- cotransporter in the distal renal tubule) but with differing potency. The maximal recommended doses are 25 mg of chlorthalidone and 50 mg of hydrochlorothiazide; side effects increase beyond these doses with little further antihypertensive effect.

Loop diuretics are short-acting agents and as such do not have a role in the management of hypertension aside from use in patients with clinically significant fluid retention. In the setting of CKD stage 4 and greater (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2), thiazides lose potency, and loop diuretics may often be required.

Agents that act at the distal Na^+ channel in the renal tubule ("potassium-sparing diuretics" such as spironolactone, eplerenone, and amiloride) are weaker diuretics than thiazides and are often reserved for treatment of aldosterone-mediated hypertension or resistant hypertension. Because the mechanism of action of these agents predisposes to hyperkalemia, use of these agents in combination with other drugs that act on the renin-angiotensin system (ACE inhibitors, ARBs, and direct renin inhibitors) must be cautiously considered and closely monitored.

Choice of Calcium Channel Blocker

There are no evidence-based recommendations regarding selection of a dihydropyridine (amlodipine, felodipine, nifedipine) CCB versus a non-dihydropyridine (diltiazem, verapamil) CCB for the treatment of hypertension; therefore, the mechanisms of action and side-effect profiles typically dictate their utilization. Non-dihydropyridine CCBs act upon calcium channels in the heart and may lead to increased relaxation and decreased atrioventricular node conduction, whereas dihydropyridine CCBs act upon calcium channels of the vasculature, increasing vasodilation.

Of note, there is an FDA safety alert regarding the use of statins together with CCBs. Specifically, the use of simvastatin at doses 10 mg and above and lovastatin at doses 20 mg and above is contraindicated with verapamil or diltiazem, and simvastatin at doses 20 mg and above is contraindicated with amlodipine due to an increased risk of myopathy.

Choice of Renin-Angiotensin System Agent

ACE inhibitors and ARBs have comparable effects upon blood pressure reduction and similar efficacy in reducing proteinuria, slowing CKD progression, and preventing cardiovascular events. The direct renin inhibitor aliskiren has similar antihypertensive efficacy but has not been extensively studied in head-to-head trials compared with other renin-angiotensin system (RAS) agents. Beyond cost considerations, the primary rationale for selecting one versus another lies in side-effect profiles. ACE inhibitors are associated with a 15% to 20% incidence of dry cough not seen with ARBs. ACE inhibitors also carry a higher rate of angioedema, a rare but life-threatening side effect. Angioedema can occur with direct renin inhibitors at rates similar to ACE inhibitors, whereas the risk of angioedema with ARBs is only slightly higher than with the use of β-blockers. Individuals with a history of angioedema or who develop angioedema on an ACE inhibitor or a direct renin inhibitor may (with great caution) be tried on ARBs, with a small risk of recurrence. All RAS agents are contraindicated in pregnancy due to fetal urogenital developmental abnormalities.

TABLE 22. Potential Factors that Influence the Selection of an Initial Antihypertensive Agent

Agent	Potential Clinical Indications	Potential Clinical Contraindications
Thiazide diuretic	Isolated systolic hypertension in elderly; hypertension in black patients; heart failure	Gout; hyponatremia; glucose intolerance; concomitant lithium use
ACE inhibitor/ARB	Heart failure; post-MI; CKD; proteinuria; diabetes mellitus/metabolic syndrome	Pregnancy[a]; hyperkalemia; bilateral renal artery stenosis
CCB	Isolated systolic hypertension in elderly; hypertension in black patients	Heart failure (non-dihydropyridines)
β-Blocker	Post-MI; heart failure; tachyarrhythmia; pregnancy; angina (NOT recommended for initial use except under these conditions)	Peripheral arterial disease; COPD; glucose intolerance

ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; MI = myocardial infarction.

[a]Absolute contraindication.

TABLE 23. Frequently Used Antihypertensive Medications

Class/Agent	Dose/Frequency	Common Side Effects
Thiazide Diuretics		**Hypokalemia; hyponatremia; hyperlipidemia; hyperuricemia; hyperglycemia**
Hydrochlorothiazide	12.5-50 mg daily	
Chlorthalidone	12.5-25 mg daily	
ACE Inhibitors		**Hyperkalemia; cough**
Captopril	25-75 mg three times daily	
Lisinopril	5-40 mg daily	
Enalapril	5-20 mg twice daily	
Benazepril	10-40 mg daily	
Angiotensin Receptor Blockers		**Hyperkalemia**
Candesartan	4-32 mg daily	
Losartan	25-100 mg daily	
Valsartan	40-320 mg daily	
Irbesartan	75-300 mg daily	
Calcium Channel Blockers		
Dihydropyridines		
Amlodipine	2.5-10 mg daily	Pedal edema
Felodipine	2.5-10 mg daily	Headache
Nifedipine (extended release)	30-180 mg daily	
Non-dihydropyridines		
Diltiazem (extended release)	120-360 mg daily	Constipation
Verapamil (extended release)	120-480 mg daily	
β-Blockers		**Fatigue; bronchospasm; sexual dysfunction; hyperglycemia**
Atenolol	25-100 mg daily	
Metoprolol tartrate	25-100 mg twice daily	
Metoprolol succinate	25-200 mg daily	
Labetalol	100-600 mg three times daily	
Potassium Channel Openers (Vasodilators)		**Edema**
Hydralazine	25-75 mg three times daily	Lupus-like syndrome
Minoxidil	2.5-10 mg twice daily	Hypertrichosis
α-Blocker		**Orthostatic hypotension; dizziness**
Prazosin	1-10 mg twice daily	
Central α-Agonists		**Fatigue; depression; rebound hypertension**
Clonidine, oral	0.1-0.4 mg twice daily	
Clonidine, patch	0.1-0.3 mg/24 h applied once every 7 days	
Potassium-Sparing Diuretics		**Hyperkalemia**
Spironolactone	25-50 mg daily	Gynecomastia
Amiloride	5 mg daily or twice daily	
Eplerenone	50 mg daily or twice daily	

The use of dual RAS agents (ACE inhibitor, ARB, or the direct renin inhibitor aliskiren) is not recommended (see next section).

Combination Therapy

There is general agreement that a single antihypertensive agent or lifestyle modification alone is unlikely to control blood pressure in patients who are >20/10 mm Hg above target blood pressure. In this circumstance, initial therapy may include lifestyle modification with a combination of agents either separately or in a fixed-dose pill. A thiazide diuretic in combination with an ACE inhibitor or ARB is commonly employed, as is the combination of an ACE inhibitor or ARB with a CCB. These combinations have been supported by both the JNC 8 and European Society of Hypertension as reasonable approaches to management. Although no definitive recommendations exist regarding the best combination of agents to employ, there is some evidence that an ACE inhibitor/CCB combination may be more effective than an ACE inhibitor/thiazide combination. Combination of a thiazide and CCB is also an effective strategy, although there have not been large clinical trials comparing this combination to other combination therapies. Conversely, the use of dual RAS agents (ACE inhibitor, ARB, or the direct renin inhibitor aliskiren) is not recommended because of lack of benefit in renal or cardiovascular end points and increased adverse events.

Assessment of Efficacy and Medication Titration

After lifestyle modification and a pharmacologic treatment regimen have been implemented, patients should be assessed monthly until blood pressure goals have been achieved.

As antihypertensive agents are titrated or added when there is inadequate blood pressure control, it is important to recognize that there is a nonlinear and diminishing blood pressure–lowering effect when titrating from 50% maximal dose to 100% maximal dose of any agent. A general rule of thumb is that 75% of an agent's blood pressure–lowering effect may be achieved with 50% of its maximal dose. If blood pressure control requires an additional >5 mm Hg reduction, it is unlikely to be achieved by increasing the single agent from 50% to 100% maximal dose. A combination of two agents at moderate dose is often more successful at achieving blood pressure goals than one agent at maximal dose. This strategy also minimizes the side effects that are more commonly noted at higher doses.

KEY POINTS

HVC
- Modification of diet and activity can produce blood pressure reductions that are equivalent to antihypertensive agents.
- The eighth report of the Joint National Committee recommends a blood pressure goal of <140/90 mm Hg in adult patients <60 years of age and a goal of <150/90 mm Hg for those ≥60 years of age.

(Continued)

KEY POINTS *(continued)*

- The eighth report of the Joint National Committee recommends as initial therapy of hypertension in the general nonblack population the use of any one of four drug classes: thiazide diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers.
- For patients whose blood pressure is >20/10 mm Hg above target blood pressure, initial treatment may include combination therapy.
- A combination of two hypertensive agents at moderate dose is often more successful at achieving blood pressure goals than one agent at maximal dose, which can help minimize the side effects more commonly noted at higher doses. HVC

White Coat Hypertension

The term *white coat hypertension* (also known as isolated clinic hypertension or office hypertension) is applied to patients with average blood pressure readings in the office ≥140/90 mm Hg and out-of-office readings <135/85 mm Hg as determined by home measurements or ABPM. Prevalence may be as high as 10% to 20% of patients diagnosed with hypertension. Whenever possible, ABPM should be employed to confirm the diagnosis. Although small reports suggest an increased risk of stroke in patients with white coat hypertension compared with normotensive individuals, there does not appear to be increased cardiovascular risk when studies are pooled in meta-analyses. However, white coat hypertension is associated with an increased likelihood of progressing to hypertension, therefore justifying evaluation for other risk factors, lifestyle modification, and close monitoring. In addition to the evaluation of hypertension (see Testing), screening echocardiography may be beneficial in this setting to determine early end-organ manifestations of hypertension that might guide therapy.

Masked Hypertension

Patients with masked hypertension have normal office blood pressure measurements but elevated blood pressure (>135/85 mm Hg) in the ambulatory setting. ABPM should be considered in such patients, especially in the presence of other cardiovascular risk factors or target organ damage. Although prospective trials are lacking, treatment of masked hypertension with lifestyle modification, and pharmacologic agents if necessary, should be considered to achieve ambulatory blood pressure <135/85 mm Hg.

Resistant Hypertension

Treatment-resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic. Prevalence can be as high as 10%. The approach to this condition begins with the elimination of "pseudoresistance" (inappropriate blood pressure measurement techniques, sclerotic noncompressible arteries, the presence of white coat hypertension, or poor patient medication adherence). After these factors have been eliminated, a search for identifiable causes of hypertension should be undertaken (**Table 24**). Screening for significant alcohol intake should also be performed.

The addition of a diuretic is critical before diagnosing a patient as having resistant hypertension. The combination of a calcium channel blocker, RAS agent, and diuretic is synergistic. Adding a low-dose aldosterone antagonist (such as spironolactone or eplerenone) may improve blood pressure control. Chronotherapy (moving at least one long-acting medication to nighttime) has been shown to restore dipping, which is associated with lower cardiovascular events. Although other vasodilators (such as hydralazine or minoxidil) and centrally acting agents (such as clonidine or guanfacine) have been used, side effects are common; these drugs are reserved for patients with the most resistant hypertension.

TABLE 24. Identifiable Causes of Hypertension and Associated Diagnostic Tests[a]

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing syndrome (most commonly due to chronic exogenous glucocorticoid therapy)	Overnight dexamethasone suppression test (not necessary if the patient is on chronic glucocorticoid therapy) or 24-hour urine free cortisol; late evening salivary cortisol
Drug-induced/related	Drug screening
Pheochromocytoma	24-Hour urine metanephrines and 24-hour urine catecholamines; if preclinical suspicion is high, measure plasma free metanephrines instead
Hyperaldosteronism	Plasma aldosterone-plasma renin activity ratio, measured midmorning in an ambulatory patient who is euvolemic and normokalemic
Renovascular hypertension	Doppler flow study; MR or CT angiography
Sleep apnea	Polysomnography
Thyroid dysfunction	TSH level
Primary hyperparathyroidism	Serum calcium level

GFR = glomerular filtration rate; TSH = thyroid-stimulating hormone.

[a]Diagnostic testing for causes of secondary hypertension should be guided by history and physical examination findings consistent with the secondary cause being considered.

KEY POINT

- Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic.

Secondary Hypertension

Identifiable (secondary) causes of hypertension are discovered in 2% to 10% of patients with hypertension; consequently, all patients with hypertension do not need to be screened unless a potential cause is suggested based on the history, physical examination, or the recommended initial laboratory testing for patients with newly diagnosed hypertension. Possible situations in which screening for identifiable causes should be considered include the following: young age of onset (in childhood or adolescence), especially in the absence of family history; severe or resistant hypertension; abrupt worsening of blood pressure in a previously well-controlled patient; or clinical features of an underlying disorder associated with hypertension (see Table 24).

Kidney Disease

Pathophysiology and Epidemiology

Both acute and chronic kidney disease are the most common identifiable conditions associated with hypertension. More than 80% of patients with late-stage CKD are hypertensive. The pathophysiology of hypertension in kidney disease is complex, but sodium retention is the predominant mechanism and is related to a reduction in GFR, resistance to natriuretic peptides, and increased activity of the renin-angiotensin-aldosterone system. Impaired nitric oxide availability and sympathetic overactivity are also thought to play significant roles in causing hypertension. Uncontrolled hypertension is an important correctable factor associated with CKD progression.

Clinical Manifestations

The prevalence of hypertension increases with progressive reduction in GFR. Patients may have edema, but hypervolemia may be present despite the absence of edema.

Diagnosis

Because of the strong association of hypertension with kidney disease, measurement of renal indices, including serum creatinine and urine albumin, is recommended during the initial evaluation of all patients diagnosed with hypertension. Kidney ultrasonography is recommended if kidney function is impaired, if there is suspicion for fibromuscular dysplasia, or if there is a family history of polycystic kidney disease. Additional diagnostic testing is based on urinalysis and imaging results.

Management

The JNC 8 recommends a blood pressure goal of <140/90 mm Hg for patients with CKD, with or without diabetes. The Kidney

Disease: Improving Global Outcomes (KDIGO) guidelines suggest a lower blood pressure goal of <130/80 mm Hg in patients with proteinuria >500 mg/g.

In patients with CKD and hypertension, JNC 8 recommends use of an ACE inhibitor or ARB as initial or add-on therapy if not contraindicated, regardless of race, although special considerations may apply to black patients (see Special Populations). An increase in the serum creatinine of up to 30% is acceptable with the use of ACE inhibitors or ARBs, but if a more severe decline in kidney function occurs, overdiuresis or the presence of bilateral renal artery stenosis should be considered.

Control of sodium balance is an essential component of blood pressure management in patients with kidney disease. Dietary sodium restriction to <2000 mg/d combined with appropriate use of diuretics is advised. As the GFR declines (especially <30 mL/min/1.73 m^2), thiazide diuretics become less effective. Loop diuretics should be employed in such patients, with doses titrated to clinical response. Other drugs effective in kidney disease are CCBs. Nocturnal administration of at least one long-acting antihypertensive medication is recommended to restore the normal fall in blood pressure at night (chronotherapy), which is frequently absent in patients with CKD and hypertension. In patients with a GFR <15 mL/min/1.73 m^2, blood pressure may improve with better volume control associated with initiation of dialysis.

Renovascular Hypertension

Pathophysiology and Epidemiology

Renovascular disease is not invariably associated with renovascular hypertension. Although renovascular disease may be seen in a significant proportion of patients with hypertension, the true incidence of renovascular hypertension is unknown. The pathogenesis of hypertension in the acute stage of renal artery stenosis relates to hypoperfusion of the kidney, leading to release of renin and angiotensin and subsequent systemic vasoconstriction and hypertension. Renin and aldosterone levels are typically high at this stage. With damage to the contralateral kidney or with bilateral renal artery stenosis, the pathogenesis switches to a volume-dependent hypertension with normal or low renin levels. Correcting the stenosis at this stage may not lead to improvement in blood pressure because there may be irreversible parenchymal damage in the affected kidney from chronic ischemia or the contralateral kidney from the effects of hypertension.

Most patients with renovascular disease (>90%) have atherosclerosis. In younger patients, especially women, fibromuscular dysplasia may be seen (**Figure 11**).

Clinical Manifestations

Recurrent episodes of "flash" pulmonary edema or a marked elevation in serum creatinine with control of blood pressure, especially with the use of an ACE inhibitor or ARB, suggests renovascular disease. The presence of a renal bruit is insensitive in the diagnosis of renal artery stenosis, but hypertension

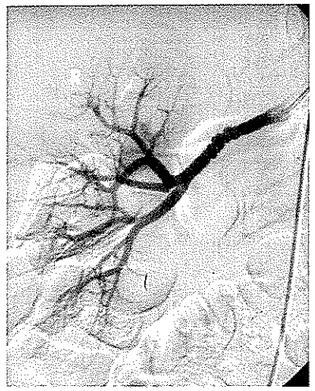

FIGURE 11. Renal angiogram showing typical fibromuscular dysplasia. This noninflammatory, nonatherosclerotic disorder of unclear etiology most commonly affects the arterial media, causing distortion of the arterial wall ("string of beads" sign) that may result in renal artery stenosis.

and a systolic/diastolic abdominal bruit is associated with a positive likelihood ratio of 4.8.

Diagnosis

Duplex Doppler of the renal arteries is an effective screening test when performed in an experienced vascular laboratory. However, MR or CT angiography may be required to confirm the anatomic diagnosis. The gold standard is renal arteriography, but in view of significant side effects, this is undertaken only if an intervention to correct a discovered stenosis is planned. Peripheral renin and aldosterone profiling are generally not helpful in later stages of renovascular disease.

Management

No clinical trials have demonstrated that percutaneous intervention (angioplasty or stenting) to improve blood flow to the stenotic kidney results in improvement of hypertension or a lessening of kidney deterioration. Thus, medical management, including correction of modifiable cardiovascular risk factors, is the primary therapeutic intervention in most patients with renal artery stenosis. Percutaneous intervention may be considered in select patients such as those with a short duration of hypertension, recurrent flash pulmonary edema with bilateral renal artery stenosis, and in young women with fibromuscular dysplasia.

Hypokalemia and Hypertension

Hyperaldosteronism, usually from an aldosterone-producing adenoma or bilateral idiopathic hyperaldosteronism, may be present in up to 10% of patients with hypertension. Hypokalemia in the absence of diuretic therapy or in response to low-dose thiazide therapy is an important clue to the presence of this disorder, although not all patients with hyperaldosteronism have hypokalemia. The plasma aldosterone-plasma

CONT.

renin activity ratio (ARR) is used to evaluate for this condition if suspected (see Table 24). Many medications can interfere with interpretation of the ARR; testing can therefore be challenging because discontinuing hypertensive medications in patients with refractory hypertension can be difficult. Spironolactone and diuretics should be stopped before testing for 4 to 6 weeks and several days, respectively. See MKSAP 17 Endocrinology and Metabolism for details on primary hyperaldosteronism.

An important differential diagnosis in patients with hypokalemia and hypertension are disorders associated with mutation of sodium channels in the distal nephron and other disorders of adrenal steroid synthesis. This group of disorders includes Liddle syndrome, syndrome of apparent mineralocorticoid excess, and familial hyperaldosteronism type 1 (also known as glucocorticoid-remediable hyperaldosteronism). In these disorders, severe early-onset hypertension associated with hypokalemia is present, but renin and aldosterone levels are suppressed because of primary sodium absorption.

Pheochromocytoma

Catecholamine-secreting tumors of chromaffin cells of the adrenal medulla (pheochromocytomas) and the sympathetic ganglia (extra-adrenal pheochromocytomas or paragangliomas) cause hypersecretion of norepinephrine and epinephrine, leading to hypertension. Patients present with symptoms of sympathetic overactivity. Screening tests for urine catecholamines and metanephrines should be performed, followed by imaging to localize the suspected tumor. Surgical removal is the only definitive treatment. See MKSAP 17 Endocrinology and Metabolism for details on pheochromocytoma.

KEY POINTS

- The eighth report of the Joint National Committee recommends a blood pressure goal of <140/90 mm Hg in patients of all ages who have chronic kidney disease with or without diabetes mellitus.
- Blood pressure management in patients with kidney disease includes the use of an ACE inhibitor or angiotensin receptor blocker as well as control of sodium balance.

HVC
- Medical management is the primary therapeutic intervention in most patients with renal artery stenosis.

Special Populations

Women

Although the prevalence of hypertension in women is lower before the age of 50 years, the eventual prevalence is similar to men. Hypertensive complications are lower in women (especially coronary artery disease). The response to hypertensive therapy is similar to men, but women derive much better cardiovascular benefit.

Oral contraceptives may be associated with overt hypertension in up to 5% of women. Stopping the drug usually leads to return of the blood pressure to baseline.

ACE inhibitors, ARBs, and aldosterone blockers should be avoided in women who are likely to become pregnant and are contraindicated in pregnant women.

Patients with Diabetes Mellitus

The JNC 8 and the American Diabetes Association both recommend a goal blood pressure of <140/90 mm Hg in patients with diabetes who are hypertensive. More aggressive lowering of the systolic blood pressure to <120 mm Hg in patients with type 2 diabetes at increased cardiovascular risk resulted in no significant cardiovascular benefit (except for a reduction in stroke) in the ACCORD study. In patients with moderately increased albuminuria or overt nephropathy (proteinuria >500 mg/g), a goal blood pressure of <130/80 mm Hg is suggested per the KDIGO guidelines.

In the absence of CKD, first-line therapy in nonblack patients with diabetes is similar to treatment of patients without diabetes: a thiazide diuretic, CCB, ACE inhibitor, or ARB. In black patients with diabetes, a thiazide diuretic or CCB is recommended for initial therapy. β-Blockers and α-blockers are not recommended as initial therapy for either group. Combination therapy of ACE inhibitors, ARBs, and direct renin inhibitors should not be used in patients with diabetes because of the increased risk of acute kidney injury and hyperkalemia without demonstrated benefit in long-term renal and cardiovascular outcomes. See Table 22 for more information.

Black Patients

Hypertension is more prevalent in black patients and associated with higher cardiovascular and renal complications than in other racial groups. The JNC 8 recommends a blood pressure goal for black patients of <140/90 mm Hg (for age ≥60 years, the target is <150/90 mm Hg, regardless of race).

A thiazide diuretic or a CCB alone or in combination is recommended as initial therapy. A potential conflict may occur with this recommendation and the guidance to use either an ACE or ARB in patients with CKD. To address this, the JNC 8 recommends that initial therapy in black patients with CKD and proteinuria be with an ACE inhibitor or ARB; in black patients without proteinuria, treatment options include a thiazide diuretic, CCB, ACE inhibitor, or ARB. See Table 22 for more information.

Older Patients

The prevalence of hypertension can be as high as 60% to 80% in patients >65 years. Frailty, sluggish baroceptor reflexes, and orthostasis are frequently seen in the elderly population. Isolated systolic hypertension (systolic >160 mm Hg and diastolic <90 mm Hg) is more common in such patients. A lower diastolic blood pressure may be associated with worse cardiovascular outcomes in epidemiologic studies, but this has not been seen in

clinical trials; thus, there are no firm recommendations for the optimal level of diastolic blood pressure below which organ perfusion (especially coronary) is impaired. The JNC 8 treatment goal for patients ≥60 years is <150/90 mm Hg. For older patients being treated for isolated systolic hypertension, the Systolic Hypertension in the Elderly Program recommends that the diastolic blood pressure be maintained above 60 mm Hg.

The choice of antihypertensive agents is similar to the general population, but a thiazide diuretic or a long-acting CCB may be more effective. ACE inhibitors or ARBs can also be used (see Table 22). Older patients are more prone to develop hyponatremia from thiazides, and the dose of medications to control blood pressure may be lower than in younger patients. Orthostasis and subsequent falls are common in older persons, and drugs that are associated with worsening or causing orthostasis (such as α-blockers, vasodilators, and centrally acting agents) should be avoided if possible.

A recent study defining frailty as the inability to walk 6 meters in less than 8 seconds demonstrated no association with hypertension and mortality, and, in those who were unable to complete the walk test, a reduction in mortality was noted with increased blood pressure. This suggests that the risk of complications, morbidity, and mortality related to lower blood pressure in frail individuals may supersede the potential benefit of lower blood pressure goals.

KEY POINTS

- ACE inhibitors, angiotensin receptor blockers, and aldosterone blockers should be avoided in women who are likely to become pregnant and are contraindicated in women who are pregnant.
- In the absence of chronic kidney disease, first-line therapy of hypertension in nonblack patients with diabetes mellitus is similar to treatment of patients without diabetes: a thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker.
- In black patients with hypertension, a thiazide diuretic or calcium channel blocker alone or in combination is recommended as initial therapy.
- The treatment goal for patients with hypertension who are ≥60 years is <150/90 mm Hg.

Chronic Tubulointerstitial Diseases

Pathophysiology and Epidemiology

Tubulointerstitial diseases primarily affect the tubules and/or interstitium of the kidney. Acute interstitial nephritis is an inflammatory process affecting the kidney interstitium and is associated with acute kidney injury (AKI) over the course of days to weeks, whereas chronic tubulointerstitial diseases develop over months to years and are a cause of slowly declining kidney function. Chronic tubulointerstitial diseases most commonly result from previous injury due to acute interstitial nephritis, but can also result from other glomerular, vascular, or obstructive diseases that may cause irreversible injury to the tubules and interstitium, even with treatment and resolution of the initial disease process. They are difficult to manage because of the diverse causes, an insidious presentation typically occurring over months to years, and often indeterminate findings on examination and laboratory testing; careful and meticulous evaluation is therefore essential. See **Table 25** for causes of tubulointerstitial diseases. See Acute Kidney Injury for more information on acute interstitial nephritis.

KEY POINT

- Chronic tubulointerstitial diseases most commonly result from previous injury due to acute interstitial nephritis, develop over months to years, and result in slowly declining kidney function.

Diagnosis and Evaluation

Symptoms and physical findings in patients with tubulointerstitial disease can be minimal or absent unless an active associated disease is present. Thus, the diagnosis is often triggered by abnormalities detected on laboratory testing performed for other purposes. History and physical examination should focus on conditions associated with tubulointerstitial disease and potential treatable causes. A careful review of medications is particularly important (see Table 25).

Many patients with chronic tubulointerstitial disease already have advanced kidney disease at the time of detection. Laboratory studies reflect the consequences of tubular dysfunction associated with these diseases. Urinalysis may be bland, often without the sterile pyuria and leukocyte casts associated with acute interstitial nephritis. Proteinuria may be present but is typically <2000 mg/24 h. Abnormal handling of glucose, amino acids, uric acid, phosphate, and bicarbonate (termed *Fanconi syndrome*) may be present, and renal tubular acidosis (RTA) is common. Patients often have concentrating defects and may present with nocturia and polyuria. With more advanced disease, anemia may be present due to the destruction of erythropoietin-producing cells in the kidney. Ultrasound can show atrophic kidneys consistent with chronicity. The role of kidney biopsy in diagnosing chronic tubulointerstitial disease is uncertain but may be appropriate in selected patients.

See **Table 26** for more information on the clinical manifestations of chronic tubulointerstitial disease.

KEY POINT

- Chronic tubulointerstitial disease should be considered in patients with slowly progressive or stable chronic kidney disease of unclear cause associated with bland urine sediment, proteinuria <2000 mg/24 h, and atrophic kidneys on ultrasound.

TABLE 25. Causes of Chronic Tubulointerstitial Diseases

Autoimmune Disorders
Anti-tubular basement membrane antibody-mediated tubulointerstitial nephritis
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
IgG4-related disease
Tubulointerstitial nephritis with uveitis (TINU)[a]
Toxic Causes
Balkan endemic nephropathy/aristolochic acid nephropathy (with increased risk of transitional cell carcinoma)
Heavy metal nephropathy (e.g., lead, cadmium, mercury)
Hereditary Tubulointerstitial Nephritis
Medullary cystic kidney disease
Mitochondrial disorders
Nephronophthisis
Infection-Related Causes
Polyoma BK virus (most commonly post-kidney transplantation)
Brucellosis
Cytomegalovirus
Epstein-Barr virus
Fungal infections
Legionella species
Mycobacterium tuberculosis
Toxoplasmosis
Chronic pyelonephritis
Malignancy-Related Causes
Leukemia
Lymphoma
Malignancy-associated monoclonal gammopathies (e.g., multiple myeloma, plasmacytoma)
Medication-Induced Causes
Analgesic nephropathy
Phosphate nephropathy
Oxalate nephropathy
Calcineurin inhibitors
Cyclooxygenase-2 inhibitors
Lithium
NSAIDs
Prolonged exposure to any medication that can cause acute interstitial nephritis: 5-aminosalicylates (e.g., mesalamine); allopurinol; cephalosporins; fluoroquinolones; H_2 blockers; indinavir; penicillins; proton pump inhibitors; rifampin; sulfonamides
Secondary Tubulointerstitial Injury Due to Glomerular and Vascular Disorders (e.g., hypertensive nephrosclerosis)
Urinary Tract Obstruction

[a]TINU is an uncommon immune-mediated syndrome with the combination of tubulointerstitial nephritis and uveitis associated with autoimmune disorders, including hypoparathyroidism, thyroid disease, IgG4-related disease, and rheumatoid arthritis.

TABLE 26. Clinical Manifestations of Chronic Tubulointerstitial Diseases

Abnormality[a]	Cause
Decline in GFR	Obstruction of tubules; damage to microvasculature; interstitial fibrosis and sclerosis of glomeruli
Proximal tubular damage (Fanconi syndrome)	Incomplete absorption and kidney wasting of glucose, phosphate, uric acid, bicarbonate, and amino acids
Normal anion gap metabolic acidosis	Proximal and distal RTA; decreased ammonia production
Polyuria and isosthenuria	Decreased concentrating and diluting ability
Proteinuria	Decreased tubular protein reabsorption (usually <2000 mg/24 h)
Hyperkalemia	Defect in potassium secretion (type 4 [hyperkalemic] distal RTA)
Hypokalemia	Defect in potassium reabsorption (type 1 [hypokalemic] distal RTA)
Anemia	Injury to erythropoietin-producing cells in the kidney

GFR = glomerular filtration rate; RTA = renal tubular acidosis.

[a]The degree of these abnormalities depends on the extent and location of injury.

Causes

See Table 25 for a list of causes of chronic tubulointerstitial disease.

Immunologic Diseases

Various immunologic diseases are associated with tubulointerstitial disease, including Sjögren syndrome, sarcoidosis, IgG4-related disease, and systemic lupus erythematosus (SLE). The incidence and severity of kidney involvement vary with the activity of the disease and treatment of the underlying process, typically with immunosuppressive therapy.

Sjögren Syndrome

Characterized by lymphocytic and plasmacytic infiltration of the parotid, salivary, and lacrimal glands, Sjögren syndrome can produce a similar injury in other nonexocrine glands and in the kidneys. Interstitial disease is the most common kidney manifestation of Sjögren syndrome; glomerular involvement is uncommon. Diagnosis is usually made by identifying tubulointerstitial disease in the context of confirmed Sjögren syndrome, although kidney biopsy will demonstrate granuloma formation.

Sarcoidosis

The tubulointerstitial disease of sarcoidosis typically presents at the time of initial diagnosis of the disease and may be