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Summary

- Typically diagnosed by screening of an asymptomatic individual.

- Treatment of uncontrolled hypertension reduces the risks of mortality and of cardiac, vascular, renal, and cerebrovascular complications.

- Lifestyle changes are recommended for all patients: weight loss, exercise, decreased sodium intake, Dietary Approaches to Stop Hypertension (DASH) diet, and moderation of alcohol consumption.

- Choice of drug therapy is often driven by considerations related to comorbid disease, but achievement of blood pressure goal may be accomplished with a variety of therapeutic agent(s).
Definition

Essential hypertension is defined as blood pressure (BP) ≥140/90 mmHg, with no secondary cause identified.[1] [2] [3] The main goal of treatment is to decrease the risk of mortality and of cardiovascular and renal morbidity.[4]

The Eighth Joint National Committee (JNC 8) guideline recommends starting pharmacologic treatment in patients with chronic kidney disease and diabetes if BP ≥140/90 mmHg.[3] In the general population aged ≥60 years, treatment to lower blood pressure should begin when BP ≥150/90 mmHg. The latter recommendation was not agreed upon by all panel members because of the risk of cardiovascular events associated with BP ≥140/90 mmHg.

In the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines, hypertension is defined as office systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, which is equivalent to a 24-hour ambulatory blood pressure measurement average of ≥130/80 mmHg, or a home blood pressure measurement average of ≥135/85 mmHg.[2]

Blood pressure goals and recommendations continue to evolve in line with new evidence.

The 2017 American College of Cardiology/American Heart Association guideline defines hypertension as any systolic blood pressure measurement of ≥130 mmHg or any diastolic BP measurement of ≥80 mmHg.[5] This definition differs from the JNC 8, ESC, and ESH guidelines.

The SPRINT trial (Systolic Blood Pressure Intervention Trial) found that a lower systolic target of 120 mmHg (as measured by automated office blood pressure) reduced cardiovascular complications and deaths in people aged over 50 years with high blood pressure and at least one additional risk factor for heart disease.[6] [7] Patients with diabetes or stroke were excluded from the trial.

Epidemiology

The prevalence of essential hypertension in the US is estimated to be about 70 million people, compared with 50 million people in 1990.[8] [9] Based on National Health and Nutrition Examination Surveys (NHANES) data, prevalence is highest in black women, who also develop hypertension at a younger age than other groups.[10] [11] Prevalence is higher in white Americans than in Mexican Americans.[11] [12] The incidence increases with age in people of all ancestries and both sexes. Prevalence is higher in men than in women before 45 years of age, equal from the ages of 45 to 64, and higher in women than in men from 65 years of age.[11] The lifetime risk is 90% for men and women who were normotensive at 55 years of age and survive to 80 years.[13] Worldwide, it is estimated that 1 billion people are hypertensive, accounting for an estimated 7.1 million deaths per year.[14]

Based on the definition of hypertension by the American College of Cardiology/American Heart Association, the prevalence of hypertension in the US increases from 32% to 46%, with over 103 million people having the condition.[5] Prevalence nearly triples among all men 20 to 44 years of age (increasing from 11% to 30%) and doubles among women younger than 45 years of age (from 10% to 19%). The prevalence of hypertension is higher in African-Americans than in white-, Asian-, and Hispanic-Americans.[5] [AHA Centers for Health Metrics and Evaluation: 2017 hypertension guidelines visualization]
**Etiology**

A multifactorial and heterogeneous etiology of essential hypertension has been proposed.\[15\] However, some initiating factors may be dampened as the hypertensive state progresses.\[16\] The following factors have been shown to disrupt the delicate balance of cardiac output and resistance, ultimately resulting in hypertension:

- Disturbance of autoregulation (reflex and persistently increasing vascular resistance to match an increased cardiac output)\[17\]
- Excess sodium intake through a variety of mechanisms\[18\] [19]
- Renal sodium retention\[20\] [21] [22] [23]
- Dysregulation of the renin-angiotensin-aldosterone axis, with elevated plasma renin activity\[24\]
- Increased sympathetic drive\[25\]
- Increased peripheral resistance\[26\]
- Endothelial dysfunction\[27\]
- Cell membrane transporter perturbations\[28\]
- Insulin resistance/hyperinsulinemia.\[29\]

**Pathophysiology**

Blood pressure (BP), the product of cardiac output and peripheral vascular resistance, is affected by preload, contractility, vessel hypertrophy, and peripheral constriction. The pathology associated with, and the perpetuation of, the hypertensive state involves structural changes, remodeling, and hypertrophy in resistance arterioles.\[16\] These changes have also been associated with the early and progressive development of small vessel atherosclerosis, which is likely the cause of end-organ damage seen in advanced hypertension. This occurs through a complex series of interrelated processes including thrombosis, endothelial injury and dysfunction, the inflammatory cascade, oxidative stress, and autonomic dysregulation in the setting of genetic predisposition.\[30\]

Trials have demonstrated the importance of systolic BP in the pathophysiology of hypertension and its associated complications, which differs from older conventional thinking.\[31\] The rise in systolic BP continues throughout life, in contrast to diastolic BP, which increases until approximately 50 years of age, tends to level off over the following decade, and may stabilize or decline subsequently.
Primary prevention

The lifetime risk for development of hypertension is high. Efforts should be made to minimize risk factors, especially in patients with pre-hypertension (defined as 120 to 139/80 to 89 mmHg); these patients should be proactively counseled to effect lifestyle modifications so as to reduce their risk of developing hypertension. The 2017 American College of Cardiology/American Heart Association guideline introduced a new category, elevated blood pressure, which is defined as 120 to 129/<80 mmHg and recommends lifestyle modification for these patients. [5] Recommended lifestyle modifications include dietary changes, smoking cessation, increased physical activity, and reduced alcohol intake.

Population-based approaches to prevent hypertension have been proposed: the American Public Health Association has advocated for reduced sodium in the food supply, particularly in processed foods. [43] Although sodium reduction has a modest effect on blood pressure lowering, the population effect on the huge number of at-risk people would potentially have significant consequences for cardiovascular morbidity and mortality. [44]

Screening

The vast majority of hypertensive patients will be detected during an asymptomatic screening during some contact with the medical system. The US Preventive Services Task Force (USPSTF) recommended yearly screening for adults aged ≥40 years or for those at increased risk for high blood pressure (BP) (high-normal BP, overweight or obese, or African-American). Adults aged 18 to 39 years with normal blood pressure (<130/85 mmHg) without other risk factors were advised to be rescreened every 3 to 5 years. The American College of Cardiology/American Heart Association (ACC/AHA) guideline, however, recommends annual screening in all patients with normal blood pressure. [5] The USPSTF recommended obtaining measurements outside of the clinical setting (ambulatory blood pressure monitoring [58] or home BP) to confirm the diagnosis. [46] The ACC/AHA guideline reinforces this recommendation differing only in the threshold. If a patient has an untreated systolic blood pressure >130 mmHg but <160 mmHg or diastolic blood pressure >80 mmHg but <100 mmHg, it is reasonable to screen for the presence of white-coat hypertension by using either daytime ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) before diagnosis of hypertension. [5] In adults with elevated office blood pressure (120-129/<80 mmHg) but not meeting the criteria for hypertension, screening for masked hypertension with daytime ABPM or HBPM is reasonable. Guidelines for other countries may recommend different screening intervals. The European Society of Cardiology/European Society of Hypertension guideline recommends annual screening for patients with high-normal BP 130 to 139/85 to 89 mmHg, at least every 3 years for patients with normal BP 120 to 129/80 to 84 mmHg and at least every 5 years for patients with optimal BP <120/80 mmHg. [2]

These screening guidelines are often exceeded, as BP measurement is standard for each encounter in many practice settings. Elevated readings should always be confirmed on a second visit prior to diagnosing hypertension.

Secondary prevention

Aggressive lifestyle modifications (dietary changes, smoking cessation, increased physical activity, reduced alcohol intake) should be initiated in patients with pre-hypertension (blood pressure 120-139/80-89 mmHg) to delay or prevent the onset of overt hypertension. The 2017 American College of Cardiology/American Heart Association guideline defines elevated blood pressure as 120 to 129/<80 mmHg and recommends lifestyle modification for these patients, which should be reassessed 3 to 6 months after initiation. [5] Other cardiovascular risk parameters should be aggressively managed. For example, statins should be used in accordance with guidelines in people with diabetes. Accordingly, patients with pre-hypertension or elevated blood pressure should be evaluated for occult cardiovascular risk by screening for diabetes or dyslipidemia with fasting blood sugar and lipid levels. Global cardiovascular risk should be assessed. [American College of Cardiology: ASCVD risk estimator plus]
Case history

Case history #1

A 64-year-old black man presents for a routine visit to establish care. He denies past medical problems, but has been told that his blood pressure was a little high. He has no complaints, takes no medications, tries to adhere to a healthy diet, and rarely exercises. He reports that over the previous 5 years he has gained 6.8 kg (15 lb). Review of systems is otherwise noncontributory. Physical exam is notable for obesity and blood pressure 172/86 mmHg. The remainder of the exam is unremarkable.

Other presentations

Essential hypertension is typically an asymptomatic disease state at its onset and time of diagnosis. It may be associated with headache or visual changes, but this is rare outside of hypertensive urgency/emergency situations.

Step-by-step diagnostic approach

Most patients diagnosed with hypertension are asymptomatic; therefore, screening is essential. Patients are usually evaluated through history, physical examination, and routine laboratory tests. The 3 objectives are to:

- Assess risk factors
- Reveal identifiable causes
- Detect target-organ damage, including evidence of cardiovascular disease.

Clinical evaluation

History may elicit family history of hypertension or coronary artery disease risk factors. It is important to assess overall cardiac risk burden.[2] The age of onset may be of value when considering etiology, as the proportion of secondary causes diminishes with increasing age. Patients at increased risk for essential hypertension include those over 60 years of age, or with diabetes, or of black ancestry.[4] [41] Excess alcohol intake or lack of exercise should be documented. A thorough medication history should be taken including screening for use of oral contraceptive pills, nonsteroidal anti-inflammatory drugs, sympathomimetics, or herbal medications. Most patients are asymptomatic, but clinical indications of hyperthyroidism, hypothyroidism or catecholamine excess (e.g., tachycardia, weight loss, sweating, or palpitations), or end-organ damage (e.g., shortness of breath, chest pain, or sensory/motor deficits) should be sought. Headache or visual changes are unusual.

The physical examination should include:[2] [5]

- Blood pressure (BP): the patient should be seated quietly for at least 5 minutes, with feet on the floor and arm supported at heart level. Caffeine, smoking, and exercise should be avoided for 30 minutes prior to exam. An appropriately sized cuff should be used and the patient’s arm should be supported (e.g., resting on a desk). The bladder should encircle at least 80% of the arm, and the width of the bladder should be at least 40% of the arm circumference. At the first visit, blood pressure should be recorded in both arms, using the arm that gives the higher reading for
subsequent visits. Two or more measurements should be made on two or more occasions and the average recorded.\[1\]\[5\] Verification should be obtained in the contralateral arm. Pre-hypertension is a reading of 120 to 139/80 to 89 mmHg,\[1\] hypertension is ≥140/90 mmHg in adults.\[3\]

- Examination of optic fundi
- Calculation of BMI from height and weight
- Auscultation for possible carotid, abdominal, or femoral bruits
- Palpation of the thyroid gland
- Examination of the heart and lungs
- Examination of the abdomen for enlarged kidneys, masses, distended urinary bladder, or abnormal aortic pulsation
- Palpation of the lower extremities for edema and pulses
- Neurologic assessment.

Physical exam may reveal end-organ damage associated with untreated hypertension: for example, retinopathy, vascular bruits, signs of congestive heart failure, evidence of aortic aneurysm (pulsatile mass/bruit), left ventricular hypertrophy (displaced point of maximal impact), or neurologic deficit(s). Absence of femoral pulses suggests coarctation of the aorta. An abdominal bruit may suggest aortic aneurysm or renal artery stenosis. Occasionally, patients may have stigmata of endocrinopathy such as Cushing disease (moon face, centripetal obesity, striae), acromegaly (acral enlargement), Graves disease (goiter, exophthalmos, pretibial myxedema), or hypothyroidism (dry skin, delayed return of deep tendon reflexes), indicating a secondary cause of hypertension.

White-coat hypertension is suspected when blood pressure readings in the office exceed those outside of the clinical setting. Ambulatory blood pressure monitoring (ABPM) may be helpful in patients with suspected white-coat hypertension, and also in cases of apparent drug resistance or episodic hypertension. Home blood pressure monitoring (HBPM) is useful for the initial diagnosis and the long-term follow-up of hypertension.\[45\] The US Preventive Services Task Force recommends out-of-office blood pressure measurement prior to diagnosis of hypertension; ABPM is the preferred method, and HBPM is an acceptable alternative.\[46\] There is no universal agreement on definitions of hypertension measured by ABPM, but European guidelines suggest a cut-off of 135/85 mmHg for daytime ABPM or home blood pressure.\[2\] Out-of-office blood pressure measurements to confirm diagnosis of hypertension are also recommended by the American College of Cardiology/American Heart Association (ACC/AHA). Corresponding values of office BP, home BP, daytime ABPM, nighttime ABPM, and 24-hour ABPM are provided by the ACC/AHA.\[5\] For example, an office BP measurement of 130/80 mmHg corresponds to home BP 130/80 mmHg, daytime ABPM 130 mmHg, nighttime ABPM 110/65 mmHg, and 24-hour ABPM 125/75 mmHg. [ACC/AHA: corresponding values of systolic blood pressure/diastolic blood pressure for clinic, home blood pressure monitoring, daytime, nighttime, and 24-hour ambulatory blood pressure monitoring measurements] Auscultatory devices (e.g., mercury, aneroid) are not generally useful for HBPM because patients rarely master the required technique for blood pressure measurement using these devices. Automated validated devices should be used instead.

Masked hypertension is suspected when out-of-office BP measurements exceed those taken in the clinical setting. In adults with elevated office BP (120-129/<80 mmHg) but not meeting the ACC/AHA criteria for hypertension, screening for masked hypertension with daytime ABPM or HBPM is reasonable.\[5\]

Automated office blood pressure (AOBP) is another option that has been designed to more accurately measure blood pressure.\[47\] Multiple measurements are taken while the patient is alone in a quiet room, sitting with legs uncrossed, back supported, and arm supported at heart level. Depending on the
device used, 3 to 6 measurements are taken over a short time period and the mean blood pressure is calculated.[48] AOBP measures about 5 mmHg lower than research-quality BPs, and 10 to 15 mmHg lower than routine office BP measurements.[49] [50] When using AOBP, hypertension is defined as ≥135/85 mmHg.

Tests

Routine metabolic panel and lipid levels are required. Glomerular filtration rate is calculated according to the Modification of Diet in Renal Disease (MDRD) formula[51]

[VIDEO: Glomerular Filtration Rate Estimate by the IDMS-Traceable MDRD Study Equation ]

or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

[VIDEO: Glomerular Filtration Rate Estimate by CKD-EPI Equation ]

In particular, features of the metabolic syndrome (hyperglycemia, dyslipidemia) or hyperuricemia should be noted. Hemoglobin and routine urinalysis with albumin excretion are also recommended for possible identification of causes of hypertension. An ECG should be obtained.

More extensive testing for secondary causes of hypertension is generally not indicated, unless BP is difficult to control or clinical or routine lab data suggest identifiable secondary causes such as signs of unprovoked hypokalemia or renal insufficiency.[2] [5] Echocardiogram and carotid Dopplers may have prognostic implications, but they are not routinely recommended except as recommended by guidelines. There was increased risk of mortality and cardiovascular events in patients with increased left ventricular mass and abnormal geometric left ventricular hypertrophy on echocardiogram.[52] [53] Increased cardiovascular events were associated with higher intima media thickness values on carotid Dopplers.[54]

Sleep study may be considered in cases of resistant hypertension, and also for patients with signs or symptoms of obstructive sleep apnea.

If secondary hypertension is suggested by history, or physical or routine laboratory testing, further testing can be performed.[2]

- Signs/symptoms of catecholamine excess require pheochromocytoma screen.
- Signs/symptoms of hyper- or hypothyroidism require thyroid-stimulating hormone.
- Unprovoked hypokalemia prompts measurement of plasma renin activity/aldosterone, catecholamines, and a search for clues (such as striae) to suggest hypercortisolism.
- Measurement of plasma aldosterone and renin is also indicated in the following situations: BP is sustained above 150/100 mmHg on 3 measurements over different days, with hypertension resistant to 3 conventional antihypertensive drugs (including a diuretic), or controlled BP (140/90 mmHg) on 4 or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (40 years); hypertensive first-degree relatives of patients with primary aldosteronism.[55]
- Renal artery imaging is done for young patients with difficult-to-control hypertension or who have abdominal bruits.[2] Imaging may show renal scarring or lesions.

[VIDEO: How to perform an ECG: animated demonstration ]
Essential hypertension

Diagnosis

Risk factors

Strong obesity

- Data from the Nurses' Health Study showed that a gain of 5 kg above weight at 18 years of age was associated with 60% higher risk of development of hypertension in middle age.\[32\] A 4.5 mmHg increase in blood pressure has been associated with each 4.5 kg (10 lb) gain in weight.\[33\] One systematic review found that risk of hypertension increased continuously with increasing body mass index, waist circumference, weight gain, and waist-to-hip and waist-to-height ratio.\[34\]

- It has been postulated that the link between obesity and hypertension is driven by increased circulating volume, leading to increased cardiac output and persistently elevated peripheral vascular resistance.\[29\]

- Obesity is associated with the metabolic syndrome, insulin resistance, and type 2 diabetes.

- Bariatric treatment of class III obesity (body mass index 40 or above) can reduce or eliminate risk factors for cardiovascular disease, with an effect on hypertension, diabetes, and dyslipidemia.\[35\] \[36\]

aerobic exercise <3 times/week

- Patients with low level of fitness had a 52% greater relative risk of hypertension at 12-year follow-up compared with those with high levels of fitness.\[37\]

moderate/high alcohol intake

- Chronic alcohol consumption of more than 1 drink per day in women and more than 2 drinks per day in men has been shown to be associated with an increased risk of blood pressure elevation.\[5\] \[39\]

metabolic syndrome

- Abdominal obesity has been specifically associated with an increased risk of hypertension, as compared with generalized obesity.\[40\]

- Insulin resistance and hyperinsulinemia are thought to contribute to the development of hypertension through a variety of inflammatory mechanisms.\[16\]

diabetes mellitus

- Hyperglycemia, hyperinsulinemia, and insulin resistance lead to endothelial damage and oxidative stress, and are independently associated with the development of hypertension.\[41\]

black ancestry

- Highest incidence of hypertension is seen in black non-Hispanic people, at all age levels.\[4\]

age >60 years

- Incidence of hypertension increases with age in people of all ancestries and both sexes.\[4\]

family history of hypertension or coronary artery disease

- Patient may have family history of hypertension or coronary artery disease risk factors.\[2\]

sleep apnea

- Studies have shown around 50% of patients with sleep apnea have essential hypertension.\[5\]

- Obstructive sleep apnea is also associated with an increased risk of resistant hypertension.\[42\]
Essential hypertension

Diagnosis

Weak
sodium intake >1.5 g/day

- Individuals show a varied tolerance for sodium intake, and reduced sodium intake has modest effect on blood pressure lowering.[18] [19]

low fruit and vegetable intake

- Modest reduction in blood pressure with 4 to 6 servings of fruits and vegetables coupled with lower sodium and fat intake (Dietary Approaches to Stop Hypertension [DASH] diet).[38]

dyslipidemia

- Risk of hypertension is increased in setting of the metabolic syndrome.

History & examination factors

Key diagnostic factors

blood pressure ≥140/90 mmHg (common)

- Aneroid, mercury, or electronic cuff. Equipment needs calibration. Auscultatory devices (e.g., mercury, aneroid) are not generally useful for home blood pressure monitoring (HBPM) because patients rarely master the required technique for blood pressure (BP) measurement using these devices.[5] White-coat hypertension is suspected when blood pressure readings in the office exceed those outside of the clinical setting. Ambulatory blood pressure monitoring (ABPM) or HBPM may be helpful in patients with suspected white-coat hypertension and is recommended routinely by some guidelines.[46] Automated office blood pressure (AOBP) is another option that has been designed to more accurately measure blood pressure. Multiple measurements are taken while the patient is alone in a quiet room and the mean blood pressure is calculated.[48] Masked hypertension is suspected when out-of-office BP measurements exceed those taken in the clinical setting. In adults with elevated office BP (120-129/<80 mmHg) but not meeting the ACC/AHA criteria for hypertension, screening for masked hypertension with daytime ABPM or HBPM is reasonable.[5]

retinopathy (common)

- Retinal vascular changes are seen commonly in longstanding hypertension.

Other diagnostic factors

headache (uncommon)

- Rarely a presenting symptom, unless hypertension is acute or in setting of hypertensive urgency.

visual changes (uncommon)

- Decreased visual acuity or floaters, papilledema (rare).

dyspnea (uncommon)

- Suggests possible congestive heart failure or coronary artery disease. Dyspnea may be an anginal equivalent, particularly in the setting of diabetes.

chest pain (uncommon)
Essential hypertension

• Suggests coronary artery disease.

sensory or motor deficit (uncommon)

• Suggests cerebrovascular disease.

Diagnostic tests

1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Normal result does not rule out coronary artery disease.</td>
</tr>
<tr>
<td></td>
<td>may show evidence of left ventricular hypertrophy or old infarction</td>
</tr>
<tr>
<td>fasting metabolic panel with estimated GFR</td>
<td>Risk of hypertension is increased if there are features of the metabolic syndrome.</td>
</tr>
<tr>
<td></td>
<td>Unprovoked hypokalemia suggests hyperaldosteronism.</td>
</tr>
<tr>
<td></td>
<td>GFR is calculated according to the Modification of Diet in Renal Disease (MDRD) formula[51]</td>
</tr>
<tr>
<td>[VIDEO: Glomerular Filtration Rate Estimate by the IDMS-Traceable MDRD Study Equation ]</td>
<td>may show renal insufficiency, hyperglycemia, hypokalemia, hyperuricemia, or hypercalcemia</td>
</tr>
<tr>
<td>[VIDEO: Glomerular Filtration Rate Estimate by CKD-EPI Equation ]</td>
<td></td>
</tr>
<tr>
<td>lipid panel</td>
<td>Risk of hypertension is increased in setting of the metabolic syndrome.</td>
</tr>
<tr>
<td></td>
<td>may show high LDL, low HDL, or high triglycerides</td>
</tr>
<tr>
<td>urinalysis</td>
<td>Increased albumin excretion suggests end-organ damage.</td>
</tr>
<tr>
<td></td>
<td>may show proteinuria</td>
</tr>
<tr>
<td>Hb</td>
<td>Anemia accompanies chronic renal failure.</td>
</tr>
<tr>
<td></td>
<td>Polycythemia may be seen with pheochromocytoma.</td>
</tr>
<tr>
<td></td>
<td>anemia or polycythemia suggests secondary cause or complication</td>
</tr>
<tr>
<td>thyroid-stimulating hormone</td>
<td>Indicated if signs/symptoms of hypo- or hyperthyroidism.</td>
</tr>
<tr>
<td></td>
<td>high or low if thyroid dysfunction</td>
</tr>
</tbody>
</table>

Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma renin activity</td>
<td>low renin suggests hyperaldosteronism</td>
</tr>
<tr>
<td></td>
<td>• Indicated when unprovoked hypokalemia present.</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| **plasma aldosterone**  
- Indicated in the following situations: BP is sustained above 150/100 mmHg on 3 measurements over different days, with hypertension resistant to 3 conventional antihypertensive drugs (including a diuretic), or controlled BP (140/90 mmHg) on 4 or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (40 years); hypertensive first-degree relatives of patients with primary aldosteronism. | high aldosterone or failure to suppress with salt loading suggests hyperaldosteronism |
| **renal duplex ultrasound/MRA renal arteries/CT angiography**  
- Young patients (age <40 years) with severe hypertension or renal artery bruits.  
- Ultrasound provides hemodynamic information and magnetic resonance angiogram (MRA) provides anatomic information, in lieu of renal angiogram. CT angiography is accurate in atherosclerotic disease. | may show renal artery stenosis, renal scarring, or lesions |
| **24-hour urine pheochromocytoma screen**  
- Indicated with symptoms/signs of catecholamine excess. | elevated catecholamines if pheochromocytoma |
| **plasma fractionated metanephrines**  
- Indicated with signs/symptoms of catecholamine excess. This test is easier to perform than 24-hour urine screen, but has a higher rate of false positives. | elevated metanephrines if pheochromocytoma |
| **24-hour urine free cortisol**  
- Indicated when stigmata of Cushing disease present. | elevated in Cushing disease |
| **sleep study**  
- Sleep study may be considered in cases of resistant hypertension and also for patients with signs or symptoms of obstructive sleep apnea. | may show results consistent with obstructive sleep apnea |
| **echocardiography**  
- Assesses left ventricular hypertrophy and left ventricular function.  
- Echocardiogram may have prognostic implications, but is not routinely recommended except as recommended by guidelines.  
- There was increased risk of mortality and cardiovascular events in patients with increased left ventricular mass and abnormal geometric left ventricular hypertrophy on echocardiogram. | increased left ventricular mass, decreased left ventricular systolic function, impaired left ventricular diastolic function, and increased left atrial size and decreased function |
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Drug-induced             | • There may be signs of acute intoxication, withdrawal, or cravings with cocaine/sympathomimetics use.  
                           | • History of treatment with or ingestion of nonsteroidal anti-inflammatory drugs, oral contraceptive pills, sympathomimetics, herbal medications (e.g., black cohosh, capsicum, ma huang), licorice, immunosuppressants (cyclosporin, tacrolimus), erythropoietin, higher dose steroids, or chemotherapeutic anti-endothelial growth factor agents (bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenib).[57] | • Drug toxicology screen may detect an illicit substance.  
                           |                                                                                        | • Hypokalemia if excessive licorice.  |
| Chronic kidney disease   | • There may be pruritus, edema, or change in urine output.                                       | • High serum creatinine.  
                           |                                                                                        | • Chronic anemia may be seen.  
                           |                                                                                        | • Renal ultrasound may identify sclerotic or polycystic kidneys.  |
| Renal artery stenosis    | • Typically younger patients with difficult-to-control hypertension or older patients at risk of atherosclerotic disease.  
                           | • Renal artery bruits may be present.                                                          | • Renal duplex ultrasound or magnetic resonance angiogram of renal arteries confirms diagnosis.  |
| Aortic coarctation       | • Differential blood pressure in upper and lower extremities. Absent femoral pulses.           | • CT, angiogram, or MRI confirms diagnosis.                                                   |
| Obstructive sleep apnea  | • Typically obese patients with daytime somnolence, snoring, or choking during sleep.         | • Polysomnography shows nocturnal oxygen desaturation.                                      |
| Hyperaldosteronism       | • Few signs and symptoms other than mild metabolic alkalosis, relative hypernatremia, potassium depletion, and elevated fasting glucose. | • Unprovoked hypokalemia.  
                           |                                                                                        | • Plasma aldosterone high.  
                           |                                                                                        | • Plasma renin low.  
<pre><code>                       |                                                                                        | • Failure to suppress aldosterone with salt loading.  |
</code></pre>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>• Dry skin, cold intolerance, weight gain, sluggishness, and goiter.</td>
<td>• Thyroid-stimulating hormone elevated in primary hypothyroidism.</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>• Heat intolerance, weight loss, hyperphagia, palpitations.</td>
<td>• Thyroid-stimulating hormone suppressed and levels of free thyroid hormones elevated.</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>• There are often no differentiating symptoms; however, renal colic, abdominal pain, or bone fracture may occur.</td>
<td>• Hypercalcemia, with elevated or inappropriately normal serum PTH.</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>• Classic symptoms and signs include weight gain, moon face, dorsocervical fat pad, abdominal striae, and easy bruisability.</td>
<td>• Abnormal dexamethasone suppression, 24-hour urine free cortisol, and/or late-night salivary cortisol.</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>• Paroxysms of hypertension, flushing, and headache.</td>
<td>• 24-hour urine screen shows elevated vanillylmandelic acid, metanephrines, and/or catecholamines.</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>• Acral (hand/foot/jaw) enlargement.</td>
<td>• Elevated insulin-like growth factor-1. Elevated serum growth hormone level, not suppressed by glucose load.</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>• Signs/symptoms of systemic lupus erythematosus, rheumatoid arthritis, sclerodactyly, or history of vasculitis.</td>
<td>• Elevated erythrocyte sedimentation rate, abnormal complement levels, positive anti-DNA, antiribonucleoprotein, anti-Smith antibodies, positive rheumatoid factor.</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>• Detected after 20 weeks' gestation in a previously normotensive patient.</td>
<td>• Urinary albumin excretion of 300mg/L/24 hours if pre-eclampsia occurs</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

**2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8)**[3]

Definitions were not specifically addressed in JNC 8, though the JNC-7 definitions were implicitly adopted. New thresholds for pharmacologic treatment were defined.
The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (2004)[1]

The categories are based on the average of two or more seated blood pressure (BP) measurements on two separate office visits.

- Normal: <120/80 mmHg
- Pre-hypertension: 120-139/80-89 mmHg
- Hypertension: ≥140/90 mmHg
  - Stage 1: 140-159/90-99 mmHg
  - Stage 2: ≥160/100 mmHg


Blood pressure is categorized in 4 levels based on an average of two or more properly taken BP measurements on two or more occasions in a healthcare setting (office setting):

- Normal BP: systolic BP <120 mmHg and diastolic BP <80 mmHg
- Elevated BP: systolic BP 120-129 mmHg and diastolic BP <80 mmHg
- Stage 1 hypertension: systolic BP 130-139 mmHg or diastolic BP 80-89 mmHg
- Stage 2 hypertension: systolic BP ≥140 mmHg or diastolic BP 90 mmHg

Hypertension Canada’s 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children[56]

Blood pressure is assessed using the following 4 approaches:

- Automated office BP: a displayed mean systolic BP ≥135 mmHg or diastolic BP ≥85 mmHg is high.
- Non-automated office BP: a mean systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is high, and a systolic BP between 130 and 139 mmHg and/or a diastolic BP between 85 and 89 mmHg is high-normal.
- Ambulatory BP monitoring: patients can be diagnosed as hypertensive if the mean awake systolic BP is ≥135 mmHg or the diastolic BP is ≥85 mmHg, or if the mean 24-hour systolic BP is ≥130 mmHg or the diastolic BP is ≥80 mmHg.
- Home BP monitoring: patients can be diagnosed as hypertensive if the mean systolic BP is ≥135 mmHg or the diastolic BP is ≥85 mmHg. If the office BP measurement is high and the mean home BP is <135/85 mmHg, it is advisable to either repeat home monitoring to confirm the home BP is <135/85 mmHg or perform 24-hour ambulatory BP monitoring to confirm that the mean 24-hour ambulatory BP monitoring is <130/80 mmHg and the mean awake ambulatory BP monitoring is <135/85 mmHg before diagnosing white-coat hypertension.
2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension[2]

Cut-offs for the definition of hypertension for specific measurements are as follows.

Office BP

- Optimal BP: systolic BP <120 mmHg and diastolic BP <80 mmHg
- Normal BP: systolic BP 120-129 mmHg and/or diastolic BP 80-84 mmHg
- High-normal BP: systolic BP 130-139 mmHg and/or diastolic BP 85-89 mmHg
- Grade 1 hypertension: systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg
- Grade 2 hypertension: systolic BP 160-179 mmHg and/or diastolic BP 100-109 mmHg
- Grade 3 hypertension: systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg
- Isolated systolic hypertension: systolic BP ≥140 mmHg and diastolic BP <90 mmHg

Ambulatory BP

- Systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg for 24-hour BP
- Systolic BP ≥135 and/or diastolic BP ≥85 mmHg for daytime ambulatory BP and home BP
- Systolic BP ≥120 and/or diastolic BP ≥70 mmHg for nighttime BP
Step-by-step treatment approach

The main goal of treatment is to decrease the risk of mortality and of cardiovascular and renal morbidity.[4]

The following recommendations are based on the Eighth Joint National Committee (JNC 8) guidelines. JNC 8 states that blood pressure (BP) goal should be <140/90 mmHg for adults ages 18-59 years, including those with diabetes or chronic kidney disease, and <150/90 mmHg in the general population beginning at age 60 years.[3] In contrast, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend a BP target of <130/80 mmHg for adults, regardless of age, with confirmed hypertension and known cardiovascular disease (CVD), or a 10-year atherosclerotic CVD risk (using the atherosclerotic CVD [ASCVD] risk estimator) of 10% or more.[5] For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target of <130/80 mmHg may be reasonable.

In the general population aged ≥60 years, the JNC 8 guideline recommends pharmacologic therapy to lower blood pressure when BP ≥150/90 mmHg.[3] However, some panel members recommended retaining the JNC 7 systolic BP goal of <140 mmHg, concluding that there was insufficient evidence to implement the less intensive target in high-risk groups, including black people, those with cardiovascular disease, and those with multiple risk factors.[61] The American College of Physicians and American Academy of Family Physicians joint guideline recommends that treatment is initiated in adults ages ≥60 years with systolic BP persistently ≥150 mmHg to achieve a target systolic blood pressure of <150 mmHg to reduce the risk for mortality, stroke, and cardiac events.[62] The joint guideline recommends considering treating adults ≥60 years old with a history of stroke or transient ischemic attack, or at high cardiovascular risk, to achieve a target systolic blood pressure of <140 mmHg.[62] The European Society of Cardiology/European Society of Hypertension guidelines recommend a desired target systolic BP of 130-139 mmHg for adults aged >65 years.[2]

Evolving treatment goals

Blood pressure goals are evolving as more studies are being carried out.[63] The SPRINT trial (Systolic Blood Pressure Intervention Trial) ended early as it found that a lower systolic target of 120 mmHg (as measured by automated office blood pressure [AOBP]) reduced cardiovascular complications and deaths in people ages over 50 years with high blood pressure and at least one additional risk factor for heart disease.[6] Patients with diabetes or stroke were excluded from the trial. However, in the HOPE-3 trial, intermediate-risk people without cardiovascular disease did not benefit from BP lowering unless in the highest tertile of starting BP (>143.5 mmHg) (as opposed to higher-risk patients in SPRINT).[65]

Because of differences in the general health of older patients, the decision to treat should be on an individual basis, and BP lowering should be gradual and carefully monitored by the physician.[2] The SPRINT trial results showed equal benefit in people ages >75 years, regardless of frailty or walking speed.[67] Patients with orthostasis at enrollment, patients with dementia, and those resident in a nursing home were excluded from the trial. One systematic review found insufficient evidence regarding the benefits of hypertension treatment for frail people >80 years of age taking multiple medications, concluding that treatment should be individualized.[68] Older patients >80 years should not be denied treatment or have treatment withdrawn solely on the basis of age.[2]

Regarding patients with concomitant diabetes mellitus, there is good-quality evidence from the ACCORD trial that very intensive BP lowering (targeting a systolic pressure <120 mmHg, as compared with targeting <140 mmHg) does not lessen risk (composite outcome: nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular cause) and may increase risk of adverse events.[69]
Diabetes Association recommends that blood pressure targets in people with diabetes and hypertension are individualized by assessing cardiovascular risk, potential adverse effects, and patient preference.[70] Targets for people with diabetes range from <130/80 mmHg for those at higher risk and <140/90 mmHg for those at lower risk; for pregnant patients with diabetes, targets of 120-160/80-105 mmHg are suggested.[70] Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease if they can be achieved without undue treatment burden. The ACC/AHA recommend a blood pressure goal of <130/80 mmHg for patients with diabetes.[5]

**Lifestyle modification**

The initial approach to a newly diagnosed patient should include a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy. Initial therapeutic measure should be lifelong lifestyle modification including:[2] [5] [14] [38] [71] [72]

- Sodium reduction (optimal goal ≤1.5 g/day)
- Potassium supplementation (3.5 to 5.0 g/day): preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion
- Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins)
- Waist circumference <40 inches (<102 cm) for men and <35 inches (<88 cm) for women; weight loss to a BMI of about 25 kg/m²
- Increased physical activity: at least 30 minutes of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes per week, as tolerated or recommended by physician
- Limited alcohol consumption: ≤2 standard drinks (<20-30 g alcohol) per day in hypertensive men; ≤1 standard drink (<10-20 g alcohol) per day in hypertensive women. Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

Advice about lifestyle modification should be given upon diagnosis and should continue concurrently with all other therapeutic measures. Prior to initiation of an exercise program, patients should discuss a plan with their healthcare provider.

Smoking cessation should always be encouraged as well, to promote general vascular health, though smoking cessation has not been associated with decreased BP.

A 3-month trial is recommended in adherent patients willing to make therapeutic lifestyle changes, prior to determining that pharmacologic therapy is necessary. Most patients will require drug therapy to achieve target BP control.

**Antihypertensive drugs**

The main classes of antihypertensives include:[2] [5]

- Diuretics:
  - Thiazide (or thiazide-like): hydrochlorothiazide, chlorthalidone, indapamide
- ACE inhibitors: lisinopril, enalapril, captopril
- Angiotensin-II receptor antagonists: candesartan, irbesartan, losartan, valsartan
Essential hypertension

**Treatment**

- Calcium-channel blockers: amlodipine, diltiazem
- Beta-blockers: metoprolol, bisoprolol, carvedilol.

Beta-blockers are not recommended for first-line treatment of hypertension except in the presence of coronary artery disease, heart failure, or atrial fibrillation.[5] The examples of antihypertensive drugs listed are common examples of drugs in each class only; other drugs are available. Some of these drugs are available in fixed-dose combination formulations. These single pill formulations simplify dosing regimens and improve adherence.[2][73]

**Drug therapy for stage 1**

The ACC/AHA guidelines define stage 1 hypertension as BP 130-139/80-89 mmHg.[5] The European Society of Cardiology/European Society of Hypertension guidelines define this category of BP as high-normal BP.[2]

For stage 1 hypertension, combination therapy or monotherapy where appropriate can be initiated.[2] The choice of antihypertensive agent is driven by efficacy, adverse-effect profile, and cost. The ACC/AHA guidelines recommend initiating a single antihypertensive agent for patients with a 10-year atherosclerotic CVD risk ≥10% or known cardiovascular disease, diabetes, or chronic kidney disease.[5] [American College of Cardiology: ASCVD risk estimator plus] European guidelines recommend initiating antihypertensive treatment with a two-drug combination, preferably a single pill combination, with the exception of patients with high-normal BP and a high cardiovascular risk or in frail older patients in whom initiating treatment with monotherapy may be appropriate.[2] In patients with high-normal BP and a high cardiovascular risk only a small reduction in BP may be required to achieve the BP target and in frail older patients baroreflex sensitivity is frequently impaired and the risk of hypotension is greater.[2] Many people with stage 1 hypertension have a constellation of other cardiovascular risk factors such as smoking or mild dyslipidemia that increase the importance of BP lowering.

If BP cannot be controlled with a single agent, a drug from a different class of antihypertensives is added.

Generally, when an ACE inhibitor would usually be chosen but is not tolerated, an angiotensin-II receptor antagonist can be substituted.

**Stage 1 hypertension: without CVD-related comorbidity or chronic renal disease, or with diabetes**

A choice among four preferred classes of drugs is recommended for initial therapy.[2][5][74]

Thiazide (or thiazide-like) diuretics have been shown to be safe and efficacious first-line therapy.[75] They also decrease renal calcium excretion, so may be a good choice for women with osteoporosis. As with all antihypertensive medications, the initial dose should be the lowest possible, and then titrated for a therapeutic effect, while observing for potential adverse effects.

Alternative first-line choices include ACE inhibitors, angiotensin-II receptor antagonists, or calcium-channel blockers, or a combination of two different drugs from these classes (excluding the combination of ACE inhibitors and angiotensin-II receptor antagonists). Alikiren, a direct renin inhibitor, is also available; however, its place in the treatment pathway is not yet clear due to concerns about risks in combination with ACE inhibitors or angiotensin-II receptor antagonists, and in the settings of diabetes or renal impairment.[6] and it is not considered to be a preferred option.
In the general black population, including those with diabetes, a thiazide (or thiazide-like) diuretic or a calcium-channel blocker is recommended as initial pharmacologic therapy. The recommendation is derived from a prespecified subgroup analysis of black patients, 46% of whom had diabetes, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial. In patients with diabetes who have increased albumin excretion, ACE inhibitors or angiotensin-II receptor antagonists are recommended. The ALLHAT study showed that chlorthalidone, amlodipine, or lisinopril were co-equal for mild hypertension in type 2 diabetes. ACE inhibitors are renoprotective, decreasing the progression of proteinuria in patients with diabetes. Sleep-time BP is the most significant independent prognostic marker of cardiovascular events in diabetes.

**Comorbid coronary artery disease**

Beta-blockers are first-line. Beta-blockers have proven beneficial in patients with chronic stable angina, post-myocardial infarction, or congestive heart failure (CHF), in patients with coronary artery disease (CAD) undergoing surgery, or in patients with hypertrophic obstructive cardiomyopathy. ACE inhibitors have been shown in some trials to decrease cardiovascular events, while other studies have not demonstrated a benefit for ACE inhibitors in the setting of stable CAD with normal left ventricular function. Beta-blockers, ACE inhibitors, or angiotensin-II receptor antagonists can be used as first-line for compelling indications (e.g., previous myocardial infarction, stable angina). Other drugs such as dihydropyridine calcium-channel blockers, thiazide diuretics, and/or mineralocorticoid receptor antagonists are added as required to further control hypertension.

Many patients with CAD also take nitrates, which act as exogenous nitric oxide donor. Modest reductions in systolic BP can be observed, but the Food and Drug Administration has not approved the use of nitrates solely as antihypertensive therapy.

**Comorbid heart failure with reduced ejection fraction**

In patients with comorbid heart failure with reduced ejection fraction (<40%), an ACE inhibitor (or an angiotensin-II receptor antagonist if not tolerated) plus a beta-blocker with or without an aldosterone antagonist is used.

ACE inhibition has been shown to convey a survival advantage in patients with CHF. Angiotensin-II receptor antagonists also decrease morbidity and mortality. Compared with ACE inhibitors, angiotensin-II receptor antagonists were equivalent, but not superior, in the treatment of patients with CHF.

Beta-blockers have proven mortality benefits in patients with chronic CHF.

Aldosterone antagonists should be given to patients with heart failure and ejection fraction under 35% who are taking optimized ACE inhibitor or angiotensin-II receptor antagonist plus beta-blocker treatment, who still require antihypertensive therapy. Blockade of aldosterone has been associated with decreased end-organ fibrosis.

Diuretics (nonaldosterone) confer no mortality benefit for patients with CHF. However, they are frequently used to relieve symptoms of fluid overload.
The combination of hydralazine and a nitrate (e.g., isosorbide dinitrate/hydralazine) has been shown to be of benefit for self-defined African Americans already taking ACE inhibitors, beta-blockers, and aldosterone antagonists, as well as in all patients with CHF who are intolerant of both ACE inhibitors and angiotensin-II receptor antagonists.[93] [94]

Nondihydropyridine calcium-channel blockers are not recommended for the treatment of hypertension in adults with heart failure with reduced ejection fraction.[5]

Sacubitril/valsartan and ivabradine are newer drugs also used for chronic heart failure.

**Comorbid heart failure with preserved ejection fraction**
Diuretics should be used to control hypertension in patients with comorbid heart failure with preserved ejection fraction (>45%) who present with symptoms of volume overload.[5] If hypertension persists after the management of volume overload, ACE inhibitors or angiotensin-II receptor antagonists and beta-blockers should be used and titrated to achieve the target BP goal.

**Comorbid left ventricular hypertrophy**
ACE inhibition has proven beneficial across a myriad of cardiovascular disease states including CHF and left ventricular hypertrophy (LVH).[84] [85] An angiotensin-II receptor antagonist is first choice for comorbid LVH. Angiotensin-II receptor antagonists have been shown to decrease morbidity and mortality in patients with hypertension and LVH.[88]

**Comorbid renal disease**
An ACE inhibitor is first choice for comorbid renal disease (chronic kidney disease stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/day or ≥300 mg/g albumin-to-creatinine ratio or equivalent in the first morning void).[5] If an ACE inhibitor is not tolerated, an angiotensin-II receptor antagonist can be used.

**Comorbid atrial fibrillation**
First choice is a beta-blocker. Second choice is a nondihydropyridine calcium-channel blocker.

Evidence from post-hoc analyses suggest that angiotensin-II receptor antagonists and ACE inhibitors do not prevent the occurrence[95] [96] or the recurrence[97] [98] of atrial fibrillation. However, more recent guidelines note that use of ACE inhibitors and angiotensin-II receptor antagonists may be effective in the prevention of atrial fibrillation.[5] [99] More investigation is needed.

**Comorbid benign prostatic hypertrophy**
The ALLHAT study conclusively demonstrated that alpha-blockers should not be a first-line antihypertensive therapy for patients with symptomatic benign prostatic hypertrophy (BPH). In these patients, the preferred first-line antihypertensive options are the same as for most other groups (i.e., thiazide-like diuretics, ACE inhibitors, angiotensin-II receptor antagonists, and calcium-channel blockers), and the alpha-blocker indication is simply to treat the BPH symptoms.

**Comorbid Raynaud disease, peripheral vascular disease, or coronary artery spasm**
Calcium-channel blockers are first choice. In addition to vascular disease, calcium-channel blockers are also useful for persistent angina or stroke prevention.[100] [101]
Stage 2 hypertension

The ACC/AHA guidelines define stage 2 hypertension as BP ≥140/90 mmHg.[5] The European Society of Cardiology guidelines define this category of BP in three grades:[2]

- Grade 1 hypertension BP 140-159/90-99 mmHg
- Grade 2 hypertension 160-179/100-109 mmHg
- Grade 3 hypertension ≥180 mmHg/110 mmHg.

Patients presenting with stage 2 hypertension will require more than one drug for BP control. Therefore, the initiation of two concurrent antihypertensives of different classes is recommended.

The combination of a nondihydropyridine calcium-channel blocker with a beta-blocker should be avoided, because of an increased risk of high-degree atrioventricular block.

Recalcitrant (resistant) hypertension

Recalcitrant (resistant) hypertension is defined as above-goal elevated BP in a patient taking three antihypertensive agents (commonly including a long-acting calcium-channel blocker, an ACE-inhibitor or angiotensin-II receptor antagonist, and a diuretic) at maximally tolerated doses.[59] Managing recalcitrant hypertension requires expertise. Frequently requiring multiple antihypertensive agents, patients must be observed and counseled regarding adverse effects, medication adherence, potential drug-drug interactions, and metabolic abnormalities. Infrequently, patients will require a screen for secondary causes of hypertension.

Representative agents of the main treatment class options, including ACE inhibitors, angiotensin-II receptor antagonists, and calcium-channel blockers, should be maximized. An optimally dosed thiazide-like diuretic, such as chlorthalidone or indapamide, should be used over hydrochlorothiazide.[59] ACE inhibitors, angiotensin-II receptor antagonists, and/or direct renin inhibitors should not be used together due to the risk of acute renal failure.

The fourth-line drug option is generally spironolactone. Eplerenone can be used as an alternative. Spironolactone and eplerenone are contraindicated in patients with hyperkalemia. Caution should be used in patients with renal impairment; either a dose adjustment may be required, or the drug may be contraindicated depending on the severity of renal impairment, indication for use (i.e., hypertension versus heart failure), and local guidance. Concomitant administration with potassium-sparing diuretics is contraindicated.

Otherwise, a safe fourth- or fifth-line option is a peripheral adrenergic blocker. Hydralazine is a less-preferred option due its twice-daily dose requirement and increased risk of edema with simultaneous calcium-channel blocker treatment. Minoxidil is rarely required in patients with advanced chronic kidney disease and its use requires some expertise in anticipating and managing side-effects of fluid retention. Combined alpha- and beta-blockers (e.g., carvedilol, labetolol) are considerations. Additionally, physicians with expertise in managing difficult-to-control hypertension have had niche success using a combination of a dihydropyridine calcium-channel blocker plus a nondihydropyridine calcium-channel blocker (e.g., amlodipine plus diltiazem). Clonidine is generally avoided because of its side-effect profile.

The most important principles for managing challenging hypertension are:

1. Promotion of medication adherence using the principle of pill reduction (i.e., use of single pill, fixed-dose combination formulations or avoidance of twice-daily dose regimens when possible)
2. Maximizing the dose of the diuretic
3. Use of spironolactone or eplerenone as a fourth drug when possible.[102]

It is also important to question the patient's alcohol use and offer lifestyle counseling.

Referral to a specialist in hypertension should be considered.

**Older adults**

In very elderly patients, many physicians are reluctant to treat hypertension in accordance with usual BP goals, for a number of reasons, including concerns about fall risk, drug interactions, adverse effects, and lack of benefit in mortality reduction. Previous literature reviews and meta-analysis demonstrated reductions in stroke, heart failure, and cardiovascular events in the very elderly without reaching mortality benefit.[103] [104] However, the SPRINT trial found that treating ambulatory adults ages 75 years or older to a systolic BP target of <120 mmHg (as measured by AOBP) resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause, compared with a systolic BP target of <140 mmHg.[67] Patients with orthostasis at enrollment, patients with dementia, and those resident in a nursing home were excluded from the trial.

The 2017 ACC/AHA guidelines recommend a systolic BP goal of <130 mmHg for noninstitutionalized ambulatory community-dwelling adults. For older adults ≥65 years of age with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.[5]

European guidelines recommend a BP target of <140/90 mmHg in all patients including independent older patients and, if treatment is tolerated, a BP target of ≤130/80 mmHg in most patients.[2]

The JNC 8 guideline recommends initiating pharmacologic therapy for patients aged ≥60 years at systolic BP ≥150 mmHg or diastolic BP ≥90 mmHg, and to treat to a systolic BP goal of <150 mmHg and a diastolic BP goal of <90 mmHg.[3]

**Pregnancy**

Treatment described in this topic is for nonpregnant patients. Management in pregnancy should be referred to an obstetrician specializing in high-risk patients.

For more information, please see our topic on Gestational hypertension.

**Implementation success**

High levels of hypertension control in large multi-ethnic populations has been demonstrated using basic principles of implementation science.[105] [106] [107] Core principles include:

1. A comprehensive hypertension registry
2. An evidence-based hypertension treatment algorithm based on single pill combination therapy
3. Free medical assistant visits for blood pressure measurement with follow-up triage, and
4. Team-based performance reporting.

The use of 2-drug combination therapy, including single pill combinations, for patients with newly diagnosed hypertension with and without comorbidities is consistent with the evidence-based JNC 8 guideline as well as the 2017 ACC/AHA guidelines and the European guidelines.[2] [5]
Essential hypertension

Given the large number of patients with hypertension and the use of protocol-based hypertension care delivery, team-based care incorporating nurses and clinical pharmacists is a key success factor.[108] [109] In team-based care collaboration, generally the role of the clinical pharmacist involves medication choice and delivery, and the role of the nurse is patient education. One randomized controlled trial demonstrated the efficacy of a low cost nurse-led email reminder program across a spectrum of cardiovascular risk factors, including lipid improvement and blood pressure reduction.[110]

The patient should be considered a hypertension team member. The TASMINH4 trial has shown that self-monitoring, with or without telemonitoring, used by general practitioners to titrate antihypertensive medication in patients with poorly controlled blood pressure, leads to significantly lower blood pressure compared with titration guided by clinic readings.[111]

An important goal is to continue to make efforts to improve disparities in blood pressure control among people of different ancestries.[112]

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

| Acute without cardiovascular disease-related comorbidity or chronic renal disease, or with diabetes |
|---|---|---|
| stage 1 hypertension | 1st thiazide diuretic plus lifestyle modification | ( summary ) 1st ACE inhibitor or angiotensin-II receptor antagonist plus lifestyle modification 1st calcium-channel blocker plus lifestyle modification 1st ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic or calcium-channel blocker plus lifestyle modification |
| stage 1 not at goal with monotherapy or stage 2 | 1st thiazide diuretic + ACE inhibitor or angiotensin-II receptor antagonist plus lifestyle modification 1st ACE inhibitor or angiotensin-II receptor antagonist + calcium-channel blocker plus lifestyle modification |
### Acute

**concomitant coronary artery disease without congestive heart failure**

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<td>calcium-channel blocker</td>
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<td>2nd beta-blocker + ACE inhibitor or angiotensin-II receptor antagonist</td>
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<td>3rd beta-blocker + thiazide diuretic</td>
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<td>3rd ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic</td>
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**concomitant heart failure with reduced ejection fraction (<40%)**

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**concomitant heart failure with preserved ejection fraction (>45%)**

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**concomitant left ventricular hypertrophy without coronary artery disease**

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<td>angiotensin-II receptor antagonist or ACE inhibitor</td>
<td>lifestyle modification</td>
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<tr>
<td>concomitant chronic renal disease without cardiovascular disease</td>
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<td>stage 1 hypertension</td>
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Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

**Acute**

without cardiovascular disease-related comorbidity or chronic renal disease, or with diabetes

- **stage 1 hypertension**
  - **1st thiazide diuretic**

  **Primary options**

  - **hydrochlorothiazide**: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses

  OR

  - **chlorthalidone**: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day

  OR

  - **indapamide**: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

  » The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

  » In several large clinical trials, no other agents have proven superior to thiazide (or thiazide-like) diuretics as monotherapy for achieving goal reductions in BP.[76]

  » May be most effective in older people and black people. Preferred initial therapy in black people.[3]

  » Given their once-daily dosing, minor adverse-effect profile, and relatively low cost, thiazide diuretics are recommended in people with diabetes without increased albumin excretion. In diabetes plus increased albumin excretion, ACE inhibitors or angiotensin-II receptor antagonists are recommended. The Antihypertensive and Lipid-Lowering Treatment to Prevent
Essential hypertension

Heart Attack Trial (ALLHAT) study showed that chlorthalidone, amlodipine, or lisinopril were co-equal for mild hypertension in type 2 diabetes.[76]

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration. If a low-to-moderate dose is not effective to reach goal, dose may be optimized or a second drug added. There is insufficient evidence about which approach is superior.

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] per day in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

1st ACE inhibitor or angiotensin-II receptor antagonist

Primary options

» lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR
### Acute

- **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses

**OR**

- **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

**OR**

- **candesartan cilexetil**: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day

**OR**

- **irbesartan**: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day

**OR**

- **losartan**: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses

**OR**

- **valsartan**: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

### The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

- May be effective in younger, especially white patients. A thiazide (or thiazide-like) diuretic or calcium-channel blocker is preferred in black people.[3]

- In patients with diabetes who have increased albumin excretion, ACE inhibitors or angiotensin-II receptor antagonists are recommended. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study showed that chlorthalidone, amlopidine, or lisinopril were co-equal for mild hypertension.
in type 2 diabetes.[76] ACE inhibitors are renoprotective, decreasing the progression of proteinuria in patients with diabetes.[78]

» Not recommended in pregnancy, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration. If a low-to-moderate dose is not effective to reach goal, dose may be optimized or a second drug added. There is insufficient evidence about which approach is superior.

» Once-daily doses may be preferred as they simplify dosing regimens and improve adherence.[73]

+ **lifestyle modification**

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly
### Treatment

**Acute**

 alcohol consumption should not exceed 140 g for men and 80 g for women.

<table>
<thead>
<tr>
<th>1st</th>
<th>calcium-channel blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>» <strong>amlodipine</strong>: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day</td>
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</tr>
<tr>
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<td></td>
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<td>OR</td>
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» The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

» Calcium-channel blockers are peripheral vasodilators.

» May be most effective in older people and black people. Preferred initial therapy in black people.[3]

» May be beneficial for some other patient groups, for example, those with Raynaud disease, peripheral vascular disease, or coronary artery spasm.

» The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study showed that chlorthalidone, amlodipine, or lisinopril were co-equal for mild hypertension in type 2 diabetes.[76]

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration. If a low-to-moderate
### Essential Hypertension

#### Treatment

<table>
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<td><strong>plus</strong> lifestyle modification</td>
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|                   | 1. sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; 
|                   | 2. Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); 
|                   | 3. maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; 
|                   | 4. increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; 
|                   | 5. limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women. |
| 1st ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic or calcium-channel blocker | **Primary options**  |
|                   | » **lisinopril**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day  |
|                   | -or-  |
|                   | » **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses  |
|                   | -or-  |
|                   | » **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day  |
|                   | -or-  |
Essential hypertension

Treatment

TREATMENT

Acute

- candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

--AND--

- hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
- chlorthalidone: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day
- indapamide: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day
- amlodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- felodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- nifedipine: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day
- diltiazem: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

Combination, low-dose therapy with an ACE inhibitor or angiotensin-II receptor antagonist plus a thiazide (or thiazide-like) diuretic or
Acute

- calcium-channel blocker is an alternative first-line option to monotherapy.

» ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

» Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.
Acute

- stage 1 not at goal with monotherapy or stage 2

1st thiazide diuretic + ACE inhibitor or angiotensin-II receptor antagonist

**Primary options**

- **hydrochlorothiazide**: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
- **chlorthalidone**: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day
- **indapamide**: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

- **AND**

- **lisinopril**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
- **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
- **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day
- **candesartan cilexetil**: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- **irbesartan**: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- **losartan**: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- **valsartan**: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

**The classification of blood pressure (BP) differs between guidelines.** For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]
ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

1st ACE inhibitor or angiotensin-II receptor antagonist + calcium-channel blocker
Acute

**Primary options**

- lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
- enalapril: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
- captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day
- candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

---AND---

- amlodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- felodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- nifedipine: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day
- diltiazem: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg. [3] [5]
### Essential hypertension

#### Treatment

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</table>
## Acute

**concomitant coronary artery disease without congestive heart failure**

- **stage 1 hypertension**

  **1st beta-blocker**

  **Primary options**

  - **metoprolol tartrate**: 50 mg/day orally (immediate-release) given in 2 divided doses initially, increase gradually according to response, maximum 200 mg/day

  - **bisoprolol**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

  - **carvedilol**: 6.25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 50 mg/day

  - The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

  - Offers cardioprotective effects in patients with coronary artery disease (CAD). Decreases myocardial wall stress and lessens myocardial oxygen demand.

  - Different agents vary in lipid solubility, selectiveness for beta-2 receptors, intrinsic sympathomimetic activity, and alpha-blocker activity. Metoprolol and bisoprolol are beta-1 selective, while carvedilol is a combined alpha- and nonselective beta-blocker.

  - May be less well tolerated in patients with reactive airways disease (COPD, asthma).

  - Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks and patients should be monitored for symptoms of angina.

  - Many patients with CAD also take nitrates, which act as exogenous nitric oxide donor.
Acute

Modest reductions in systolic BP can be observed, but the Food and Drug Administration has not approved the use of nitrates solely as antihypertensive therapy. [16]

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include: [2] [5] [14] [38] [71] [72]
  - sodium reduction (≤1.5 g/day);
  - potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion;
  - Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins);
  - maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²;
  - increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician;
  - limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

2nd calcium-channel blocker

Primary options

» amlodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

OR

» felodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

OR
Essential hypertension

**Treatment**

### Acute

- **nifedipine:** 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day

- The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

- Calcium-channel blockers are peripheral vasodilators.

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

- Avoid combination of beta-blocker with nondihydropyridine calcium-channel blockers (e.g., diltiazem or verapamil).

**plus lifestyle modification**

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [≤20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.
### Acute

- **Stage 1 not at goal with monotherapy or stage 2**

1st **beta-blocker + calcium-channel blocker**

#### Primary options

- **» metoprolol tartrate**: 50 mg/day orally (immediate-release) given in 2 divided doses initially, increase gradually according to response, maximum 200 mg/day
  - or -
  - **» bisoprolol**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or -
  - **» carvedilol**: 6.25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 50 mg/day

--AND--

- **» amlodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or -
  - **» felodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or -
  - **» nifedipine**: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day

The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]

- Beta-blockers may be less well tolerated in patients with reactive airways disease (COPD, asthma). Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, MI have occurred. All beta-blockers should be tapered over 1-2 weeks and patients should be monitored for symptoms of angina.

- Calcium-channel blockers are peripheral vasodilators.

- Avoid combination of beta-blocker with nondihydropyridine calcium-channel blockers (e.g., diltiazem or verapamil).

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.
Acute

- Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.\(^2\) [73]

**plus lifestyle modification**

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include:\(^2\) [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m\(^2\); increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

**2nd beta-blocker + ACE inhibitor or angiotensin-II receptor antagonist**

**Primary options**

- **metoprolol tartrate**: 50 mg/day orally (immediate-release) given in 2 divided doses initially, increase gradually according to response, maximum 200 mg/day
  - or -
- **bisoprolol**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or -
- **carvedilol**: 6.25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 50 mg/day
Treatment

Essential hypertension

Acute

- AND -

- lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
- enalapril: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
- captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day
- candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

- The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]

- Beta-blockers may be less well tolerated in patients with reactive airways disease (COPD, asthma). Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks and patients should be monitored for symptoms of angina.

- ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II
Acute receptor antagonist therapy continues into the second trimester.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

» Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

3rd beta-blocker + thiazide diuretic

Primary options

» metoprolol tartrate: 50 mg/day orally (immediate-release) given in 2 divided doses initially, increase gradually according to response, maximum 200 mg/day

-or-

» bisoprolol: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
Essential hypertension

| Treatment |
|-----------|-----------------|
| Acute     | -or- |
|           | » carvedilol: 6.25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 50 mg/day |
|           | -AND-- |
|           | » hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses |
|           | -or- |
|           | » chlorthalidone: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day |
|           | -or- |
|           | » indapamide: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day |

» The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]

» Beta-blockers may be less well tolerated in patients with reactive airways disease (COPD, asthma). Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks and patients should be monitored for symptoms of angina.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

» Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably...
### Treatment

#### Acute

by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

<table>
<thead>
<tr>
<th>3rd</th>
<th>ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>- lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<tr>
<td>- or-</td>
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<tr>
<td>- enalapril: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses</td>
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<tr>
<td>- or-</td>
<td></td>
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<tr>
<td>- captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day</td>
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<tr>
<td>- or-</td>
<td></td>
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<tr>
<td>- candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day</td>
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<td>- or-</td>
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<tr>
<td>- irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day</td>
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<tr>
<td>- or-</td>
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<tr>
<td>- losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses</td>
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<tr>
<td>- or-</td>
<td></td>
</tr>
<tr>
<td>- valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day</td>
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</tbody>
</table>

--AND--
Essential hypertension

Treatment

Acute

<p>| | |</p>
<table>
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</table>
|   | **» hydrochlorothiazide**: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
|   | **-or-**
|   | **» chlorthalidone**: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day
|   | **-or-**
|   | **» indapamide**: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]

ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

**plus** lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to...
### Acute

Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

<table>
<thead>
<tr>
<th>concomitant heart failure with reduced ejection fraction (≤40%)</th>
<th>1st ACE inhibitor or angiotensin-II receptor antagonist + beta-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>» lisinopril: 2.5 to 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day -or-</td>
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<tr>
<td>» enalapril: 2.5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses -or-</td>
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<tr>
<td>» captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 150 mg/day -or-</td>
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<tr>
<td>» ramipril: 1.25 to 2.5 mg orally twice daily initially, increase gradually according to response, maximum 10 mg/day -AND-</td>
<td></td>
</tr>
<tr>
<td>» carvedilol: 3.125 mg orally (regular-release) twice daily initially, increase gradually according to response, maximum 50 mg/day (or 100 mg/day in patients who weigh &gt;85 kg) -or-</td>
<td></td>
</tr>
<tr>
<td>» metoprolol succinate: 12.5 to 25 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 200 mg/day -or-</td>
<td></td>
</tr>
<tr>
<td>» bisoprolol: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day</td>
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</tr>
</tbody>
</table>
**Secondary options**

- **candesartan cilexetil**: 4-8 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
  -or-
  - **valsartan**: 20-40 mg orally twice daily initially, increase gradually according to response, maximum 320 mg/day
  --AND--
  - **carvedilol**: 3.125 mg orally (regular-release) twice daily initially, increase gradually according to response, maximum 50 mg/day (or 100 mg/day in patients who weigh >85 kg)
  -or-
  - **metoprolol succinate**: 12.5 to 25 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 200 mg/day
  -or-
  - **bisoprolol**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

- Angiotensin-II receptor antagonists may be used if ACE inhibitors are not tolerated. ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and therefore should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

- Metoprolol and bisoprolol are beta-1 selective beta-blockers; carvedilol is beta-1 and beta-2 selective and also has alpha-blocking properties. Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks, and patients should be monitored for symptoms of angina.

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

- Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2][73]

**plus** lifestyle modification
### Acute

Treatment recommended for **ALL** patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include:\[2\] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

<table>
<thead>
<tr>
<th><strong>adjunct</strong></th>
<th><strong>diuretic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for <strong>SOME</strong> patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

**Primary options**

- **furosemide**: 20-80 mg orally every 6-8 hours initially, increase gradually according to response, maximum 600 mg/day

OR

- **bumetanide**: 0.5 to 2 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

**Secondary options**

- **metolazone**: 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

- Diuretics may be used for fluid overload.
**Treatment**

### Acute

**adjunct aldosterone antagonists**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **spironolactone**: 12.5 to 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day

**OR**

- **eplerenone**: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day

- Aldosterone antagonists should be given to: patients with New York Heart Association functional class II to IV heart failure and ejection fraction <35%; or patients post-ST-elevation myocardial infarction with ejection fraction <40% and either symptomatic heart failure or comorbid diabetes. Blockade of aldosterone has been associated with decreased end-organ fibrosis.[92]

**adjunct isosorbide dinitrate/hydralazine**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **isosorbide dinitrate/hydralazine**: 20 mg (isosorbide dinitrate)/37.5 mg (hydralazine) orally three times daily initially, increase gradually according to response, maximum 120 mg (isosorbide dinitrate)/225 mg (hydralazine) per day

- Isosorbide dinitrate/hydralazine may be useful for those intolerant to or refractory to other agents.

- May offer additional mortality benefit in African American patients when added to optimized ACE inhibition plus beta-blockade plus aldosterone antagonism.[94]

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

**concomitant heart failure with preserved ejection fraction (>45%)**
### Acute

#### 1st diuretic

**Primary options**

- **furosemide**: 20-80 mg orally every 6-8 hours initially, increase gradually according to response, maximum 600 mg/day

OR

- **bumetanide**: 0.5 to 2 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

**Secondary options**

- **metolazone**: 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

**Diuretics should be used to control hypertension in patients with comorbid heart failure with preserved ejection fraction (>45%) who present with symptoms of volume overload.[5]**

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

**adjunct ACE inhibitor or angiotensin-II receptor antagonist + beta-blocker**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **lisinopril**: 2.5 to 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
- **enalapril**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
- **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 150 mg/day
- **ramipril**: 1.25 to 2.5 mg orally twice daily initially, increase gradually according to response, maximum 10 mg/day

**--AND--**

- **carvedilol**: 3.125 mg orally (regular-release) twice daily initially, increase gradually
### Essential hypertension

#### Treatment

**Acute**

- according to response, maximum 50 mg/day (or 100 mg/day in patients who weigh >85 kg)
  - or-
    - metoprolol succinate: 12.5 to 25 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 200 mg/day
    - or-
    - bisoprolol: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

**Secondary options**

- candesartan cilexetil: 4-8 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
  - or-
  - valsartan: 20-40 mg orally twice daily initially, increase gradually according to response, maximum 320 mg/day

---

- carvedilol: 3.125 mg orally (regular-release) twice daily initially, increase gradually according to response, maximum 50 mg/day (or 100 mg/day in patients who weigh >85 kg)
  - or-
  - metoprolol succinate: 12.5 to 25 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 200 mg/day
  - or-
  - bisoprolol: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

- If hypertension persists after the management of volume overload, ACE inhibitors or angiotensin-II receptor antagonists and beta-blockers should be used and titrated to achieve the target blood pressure goal.

- Angiotensin-II receptor antagonists may be used if ACE inhibitors are not tolerated. ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and therefore should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

- Metoprolol and bisoprolol are beta-1 selective beta-blockers; carvedilol is beta-1 and beta-2 selective and also has alpha-blocking properties.
Essential hypertension

Treatment

Acute

Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks, and patients should be monitored for symptoms of angina.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

» Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

<table>
<thead>
<tr>
<th>concomitant left ventricular hypertrophy without coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
</tr>
<tr>
<td>Primary options</td>
</tr>
<tr>
<td>» candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day</td>
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<tr>
<td>OR</td>
</tr>
<tr>
<td>» irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day</td>
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<tr>
<td>OR</td>
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<tr>
<td>» losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses</td>
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<tr>
<td>OR</td>
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<tr>
<td>» valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day</td>
</tr>
<tr>
<td>Secondary options</td>
</tr>
<tr>
<td>» lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<tr>
<td>OR</td>
</tr>
</tbody>
</table>
**Acute**

» **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses

**OR**

» **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

» Angiotensin-II receptor antagonists have been shown to promote regression of left ventricular hypertrophy.[113]

» An ACE inhibitor may be used as a second-line option. ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned. Pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration. Once-daily doses may be preferred as they simplify dosing regimens and improve adherence.[73]

**plus**  
**lifestyle modification**  
Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» **Lifestyle modifications should be lifelong and should include:** [2] [5] [14] [38] [71] [72]  
- sodium reduction (≤1.5 g/day);  
- potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion;  
- Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins);  
- maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²;  
- increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic
## Treatment

### Acute

- **Aerobic exercise**: Walking, jogging, cycling, or swimming on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [≤20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [≤10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

<table>
<thead>
<tr>
<th>concomitant chronic renal disease without cardiovascular disease</th>
<th>1st</th>
<th>ACE inhibitor or angiotensin-II receptor antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ <strong>stage 1 hypertension</strong></td>
<td>1st</td>
<td>ACE inhibitor or angiotensin-II receptor antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
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<td></td>
<td></td>
<td>» <strong>lisinopril</strong>: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<td>OR</td>
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<td></td>
<td></td>
<td>» <strong>enalapril</strong>: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses</td>
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<td>OR</td>
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<td></td>
<td></td>
<td>» <strong>captopril</strong>: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day</td>
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<td>» <strong>candesartan cilexetil</strong>: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day</td>
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<td>» <strong>irbesartan</strong>: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day</td>
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<td></td>
<td></td>
<td>» <strong>losartan</strong>: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses</td>
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<td>OR</td>
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</tbody>
</table>
**Acute**

- **valsartan**: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

- The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]

- ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

- A dose adjustment may be required in patients with renal impairment.

- Once-daily doses may be preferred as they simplify dosing regimens and improve adherence.[73]

**plus**  
**lifestyle modification**

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at...
Acute

least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

2nd calcium-channel blocker

Primary options

- **amlodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

OR

- **felodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day

OR

- **nifedipine**: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day

OR

- **diltiazem**: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg. [3] [5]

- Calcium-channel blockers are peripheral vasodilators.

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with
Essential hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72]
sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

2nd thiazide diuretic

Primary options

» hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses

OR

» chlorthalidone: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day

OR

» indapamide: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

» The classification of blood pressure (BP) differs between guidelines. For stage 1 hypertension, the Eighth Joint National Committee defines it as BP 140-159/90-99 mmHg and the American College of Cardiology/American Heart Association defines it as BP 130-139/80-89 mmHg.[3] [5]
## Essential hypertension

### Treatment

#### Acute

<table>
<thead>
<tr>
<th>stage 1 not at goal with monotherapy or stage 2</th>
<th>1st</th>
<th>ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic</th>
</tr>
</thead>
</table>

**Primary options**

- **lisinopril**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
  - or -
- **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses

» Thiazide (or thiazide-like) diuretics may not be as effective if glomerular filtration rate is <20 mL/minute/1.73m².

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

plus **lifestyle modification**

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:

  - Sodium reduction (≤1.5 g/day);
  - Potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

1st ACE inhibitor or angiotensin-II receptor antagonist + thiazide diuretic
Essential hypertension

Acute

» captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

--AND--

» hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
- or -

» chlorthalidone: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day
- or -

» indapamide: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

Secondary options

» candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- or -

» irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- or -

» losartan: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- or -

» valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

--AND--

» hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
- or -

» chlorthalidone: 12.5 mg orally once daily initially, increase gradually according to response, maximum 25 mg/day
- or -

» indapamide: 1.25 mg orally once daily initially, increase gradually according to response, maximum 2.5 mg/day

» The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]
**Acute**

- ACE inhibitors are first-line therapy for comorbid renal disease, with angiotensin-II receptor antagonists as an alternative. A dose adjustment may be required in patients with renal impairment.

- ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

- Thiazide (or thiazide-like) diuretics may not be as effective if glomerular filtration rate is <20 mL/minute/1.73m².

- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

- Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

**plus** **lifestyle modification**

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended
## Acute

by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

### 2nd

ACE inhibitor or angiotensin-II receptor antagonist + calcium-channel blocker

### Primary options

- **lisinopril**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
  - or-
  - **enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
  - or-
  - **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

--AND--

- **amlodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or-
  - **felodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
  - or-
  - **nifedipine**: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day
  - or-
  - **diltiazem**: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

### Secondary options

- **candesartan cilexetil**: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
  - or-
  - **irbesartan**: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
  - or-
  - **losartan**: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
  - or-
Acute

» **valsartan**: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

---AND---

» **amlodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- or -

» **felodipine**: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- or -

» **nifedipine**: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day
- or -

» **diltiazem**: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

» The classification of blood pressure (BP) differs between guidelines. For stage 2 hypertension, the Eighth Joint National Committee defines it as BP >160/100 mmHg and the American College of Cardiology/American Heart Association defines it as BP ≥140/90 mmHg.[3] [5]

» ACE inhibitors are first-line therapy for comorbid renal disease with angiotensin-II receptor antagonists as an alternative. A dose adjustment may be required in patients with renal impairment.

» ACE inhibitors and angiotensin-II receptor antagonists are not recommended in pregnancy and, therefore, should generally be avoided in women of childbearing potential because approximately half of pregnancies are unplanned, pregnancies may occur with oral contraceptive use, and there is a risk of fetopathy when ACE inhibitor or angiotensin-II receptor antagonist therapy continues into the second trimester.

» Calcium-channel blockers are peripheral vasodilators.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

» Some of these drugs are available in a fixed-dose combination formulation. These single pill formulations simplify dosing regimens and improve adherence.[2] [73]

**plus** lifestyle modification
Acute

<table>
<thead>
<tr>
<th>Concomitant atrial fibrillation without other comorbidity</th>
<th>1st beta-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>» metoprolol tartrate: 50 mg/day orally (immediate-release) given in 2 divided doses initially, increase gradually according to response, maximum 200 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» atenolol: 25-50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Following abrupt cessation of therapy with certain beta-blockers, exacerbations of angina
## Treatment

### Acute

pectoris and, in some cases, myocardial infarction have occurred. All beta-blockers should be tapered over 1-2 weeks and patients should be monitored for symptoms of angina.

- May be less well tolerated in patients with reactive airways disease (COPD, asthma).
- The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

**plus** **lifestyle modification**

Treatment recommended for ALL patients in selected patient group

- All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

- Lifestyle modifications should be lifelong and should include: sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.

### 2nd **calcium-channel blocker**

**Primary options**

- diltiazem: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

OR
Essential hypertension

Treatment

Acute

» verapamil: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

» Nondihydropyridine calcium-channel blockers (e.g., verapamil, diltiazem) are associated with negative inotropy and slowing of atioventricular conduction.

» Frequently used in the treatment of supraventricular tachycardia or atrial arrhythmias/rapid ventricular response.

» Avoid in people with decreased ejection fraction.

» The lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration.

plus lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:
  1. Sodium reduction (≤1.5 g/day);
  2. Potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion;
  3. Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins);
  4. Maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²;
  5. Increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician;
  6. Limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.
Managing recalcitrant hypertension requires expertise. Frequently requiring multiple antihypertensive agents, patients must be observed and counseled regarding adverse effects, medication adherence, potential drug-drug interactions, and metabolic abnormalities. Infrequently, patients will require a screen for secondary causes of hypertension.

Representative agents of the main treatment class options, including ACE inhibitors, angiotensin-II receptor antagonists, and calcium-channel blockers should be maximized. An optimally dosed thiazide-like diuretic, such as chlorthalidone or indapamide, should be used over hydrochlorothiazide. ACE inhibitors and angiotensin-II receptor antagonists should not be used together due to the risk of acute renal failure.

The fourth-line drug option is generally spironolactone. Eplerenone can be used as an alternative. Spironolactone and eplerenone are contraindicated in patients with hyperkalemia. Caution should be used in patients with renal impairment; either a dose adjustment may be required, or the drug may be contraindicated depending on the severity of renal impairment, indication for use (i.e., hypertension versus heart failure), and local guidance. Concomitant administration with potassium-sparing diuretics is contraindicated.

Otherwise, a safe fourth- or fifth-line option is a peripheral adrenergic blocker. Hydralazine is a less-preferred option due its twice-daily dosing requirement and increased risk of edema with simultaneous calcium-channel blocker treatment. Minoxidil is rarely required in patients with advanced chronic kidney disease and its use requires some expertise in anticipating and managing side-effects of fluid retention. Combined alpha- and beta-blockers (e.g., carvedilol, labetolol) are also considerations. Additionally, physicians with expertise in managing difficult patients have had niche success using a combination of a dihydropyridine calcium-channel blocker with a nondihydropyridine calcium-channel blocker (e.g., amlodipine plus diltiazem). Clonidine is
generally avoided because of its side-effect profile.

» The most important principles for managing the challenging patient are:

» 1) Promotion of medication adherence using the principle of pill reduction (i.e., use of single pill, fixed-dose combination formulations or avoidance of twice-daily dose regimens when possible)

» 2) Maximizing the dose of the diuretic (preferably chlorthalidone or indapamide)

» 3) Use of spironolactone as a fourth drug when appropriate.[102]

» It is also important to question the patient's alcohol use and offer lifestyle counseling.

» Referral to a specialist in hypertension should be considered.

**plus** lifestyle modification

Treatment recommended for ALL patients in selected patient group

» All patients should be given a thorough explanation of the risks associated with hypertension and the need for adequate control and adherence to therapy.

» Lifestyle modifications should be lifelong and should include:[2] [5] [14] [38] [71] [72] sodium reduction (≤1.5 g/day); potassium supplementation (3.5 to 5.0 g/day), preferably by consumption of a potassium-rich diet unless contraindicated in the presence of chronic kidney disease or use of medication that reduces potassium excretion; Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins); maintaining waist circumference of <40 inches (<102 cm) for men and <35 inches (<88 cm) for women and weight loss to a body mass index of about 25 kg/m²; increased physical activity consisting of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5 days per week to total 150 minutes/week, as tolerated or recommended by physician; limited alcohol consumption (≤2 standard drinks [<20-30 g alcohol] per day in hypertensive men, ≤1 standard drink [<10-20 g alcohol] in hypertensive women). Total weekly alcohol consumption should not exceed 140 g for men and 80 g for women.
Emerging

Renal sympathetic denervation for treatment-resistant hypertension (experimental)

Activation of renal sympathetic nerves is a component of essential hypertension pathophysiology; however, renal denervation studies have reported variable efficacy results.[115] [116] [117] [118] [119] [120] [121]

Renal denervation may be considered in the context of clinical trials, but is not used in everyday clinical practice.

Baroreflex activation therapy

Electrical stimulation of the carotid sinus baroreflex system, also known as baroreflex activation therapy (BAT), may decrease blood pressure in patients with resistant hypertension. Electric stimulators directly activating afferent baroreflex nerves have previously failed in trials for technical reasons. However, a novel implantable device may overcome some of the previously experienced technical problems. The device stimulates the carotid sinus wall and has been shown to reduce blood pressure (BP) in feasibility studies.[122] [123] [124] In the Rheos Pivotal trial, which assessed long-term blood pressure control in resistant-hypertension patients receiving BAT, BP reduction was maintained over long-term follow-up of 22 to 53 months.[125]

L-arginine supplementation

Oral supplementation with L-arginine, an amino acid and a substrate of nitric oxide synthase, has been shown to significantly lower both systolic and diastolic BP.[126]

Vitamin C supplementation

Vitamin C supplementation has been shown to reduce systolic and diastolic BP in short-term trials. Long-term trials examining the effects of vitamin C supplementation on BP and clinical events are needed.[127]

Vitamin D supplementation

Data from cross-sectional studies report that low levels of 25-hydroxy vitamin D are associated with higher systolic blood pressure and higher incidence of hypertension.[128] Large observational studies show a weaker, yet similar, association. This effect is thought to be partly mediated through regulation of the renin-angiotensin-aldosterone axis.[129] Randomized control trials conflict with observational data, probably due to differences in populations studied, doses of vitamin D used, and unmeasured confounders. A systematic review found that in studies to date, vitamin D supplementation was ineffective for blood pressure lowering.[130] Large randomized trials focusing on patients with severe vitamin D deficiency and hypertension are needed before vitamin D can be recommended for the prevention or treatment of hypertension.

Calcium supplementation

Preliminary data indicate that increased calcium intake slightly reduces systolic and diastolic blood pressure in people with normal blood pressure, particularly young people. This could have implications for prevention and public health, but more and larger studies are needed.[131]

Sodium-glucose transporter-2 [SGLT-2] inhibitors in people with type 2 diabetes

SGLT-2 inhibitors have been found to have an antihypertensive effect. Empagliflozin has been found to lower blood pressure and cardiovascular risk in people with type 2 diabetes over up to 2.6 years.[132] [133] Canagliflozin has also been associated with reduced blood pressure in people with type 2 diabetes, across a range of baseline BPs.[134]
Amiloride
In the PATHWAY-2 study of resistant hypertension, the potassium-sparing diuretic amiloride was shown to be as effective at reducing blood pressure as spironolactone, suggesting it may be an alternative option for resistant hypertension.[135]

Firibastat
In a phase II trial, firibastat, a first-in-class aminopeptidase A inhibitor, has demonstrated efficacy in lowering blood pressure in a high-risk diverse population, and may have future use in patients with difficult-to-treat or potentially resistant hypertension.[136]
Recommendations

Monitoring

While adjusting medication dosage, blood pressure (BP) should be monitored every 2 to 4 weeks. Once stabilized, BP should be checked and medications reviewed every 6 to 12 months. Serum potassium and creatinine should be checked yearly.

Patient instructions

As with most chronic conditions, hypertension requires a lifelong commitment from both patient and physician to pursue aggressive management with healthy lifestyle choices and medical therapy. Patients should be counseled about diet (Dietary Approaches to Stop Hypertension [DASH] diet, sodium ≤1.5 g/day, in consultation with a nutritionist).

- Smoking raises blood pressure (BP) acutely and transiently, but long-term studies have not found an association between smoking and the risk of developing chronic hypertension.[155] Nevertheless, smoking cessation should be encouraged to reduce cardiovascular risk.
- Acute consumption of coffee and black tea has a mild pressor effect; however, long-term studies have found slightly lower BP in patients who consume caffeine daily.[72][156] Therefore, moderate caffeine consumption is acceptable.
- Patients should be advised to begin and maintain aerobic exercise, with a goal of at least 30 minutes of moderate intensity, dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes as tolerated or recommended by a physician.
- Medication adherence is important and it should be discussed with patients in whom drug therapy for hypertension is often a lifelong commitment.

Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>coronary artery disease</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>cerebrovascular accident</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>left ventricular hypertrophy</td>
<td>long term</td>
<td>high</td>
</tr>
</tbody>
</table>

For every 20/10 mmHg increase in blood pressure (BP), there is a lifetime doubling of mortality related to ischemic heart disease or cerebrovascular accident.[144] As with all other associated complications and comorbid diseases, aggressive BP control, along with therapy specific for the individual condition, may retard the progression of disease.

The risk of developing cerebrovascular accident (CVA) varies linearly with blood pressure (BP), and BP control reduces the risk of recurrent CVA.[145]

Left ventricular hypertrophy (LVH) on echocardiography is seen in more than 30% of hypertensive patients.[149]

Linked to cardiovascular morbidity and mortality.[150] LVH patterns vary based on hemodynamic loading conditions.[151]
### Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>congestive heart failure</td>
<td>long term</td>
<td>medium</td>
</tr>
</tbody>
</table>

Patients with hypertension are 3 times more likely to develop congestive heart failure (systolic or diastolic dysfunction) as are normotensive patients.[146]

ACE inhibitors, angiotensin-II receptor antagonists, and beta-blockers confer a mortality benefit. Diuretics do not, but loop diuretics are frequently used to relieve symptoms of fluid overload.

Blockade of aldosterone has been associated with decreased end-organ fibrosis.[92]

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>retinopathy</td>
<td>long term</td>
<td>medium</td>
</tr>
</tbody>
</table>

Hypertension is associated independently with retinopathy.

Hypertension is also a major risk factor for development of other retinal vascular diseases, such as retinal vein or artery occlusion, or ischemic optic neuropathy.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>peripheral artery disease</td>
<td>long term</td>
<td>medium</td>
</tr>
</tbody>
</table>

Treatment of hypertension in patients with peripheral artery disease reduces the risk of myocardial infarction, stroke, or congestive heart failure.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronic kidney disease</td>
<td>long term</td>
<td>medium</td>
</tr>
</tbody>
</table>

Hypertension is closely associated with the development of renal disease and end-stage renal disease (ESRD). However, while many hypertensive patients will develop a mild degree of nephrosclerosis, few progress to ESRD.[152]

A more malignant course of hypertensive kidney disease is seen in black than in white people.[153]

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>aortic dissection</td>
<td>long term</td>
<td>low</td>
</tr>
</tbody>
</table>

More than 70% of patients with aortic dissection have a history of hypertension.

Despite improved methods of diagnosis and increased awareness, aortic dissection remains associated with high mortality rates, particularly proximal (type A) dissections.[147] [148]

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>malignant hypertension</td>
<td>variable</td>
<td>low</td>
</tr>
</tbody>
</table>

Undiagnosed or inadequately treated essential hypertension is the most common cause of hypertensive emergency.[154]

### Prognosis

Several trials have shown that uncontrolled hypertension is a major risk factor for the development of cardiac, vascular, renal, and cerebrovascular disease, morbidity, and mortality. However, even modest reductions in blood pressure (BP) decrease morbidity and mortality.[5] Further studies are needed to confirm optimal BP targets in diabetes.
In one randomized clinical trial (ACCORD) a more stringent blood pressure goal for patients with type 2 diabetes did not significantly reduce the primary cardiovascular outcome or most secondary outcomes compared with standard blood pressure goals. In this study, the number of total and nonfatal strokes was lower in the intensive therapy group, although the clinical benefit was limited (number needed to treat = 89 for 5 years to prevent one stroke).[69]

In patients with diabetes, the decrease in asleep blood pressure - a novel therapeutic target requiring evaluation by ambulatory monitoring - has been shown to be the most significant independent predictor of event-free survival in some studies.[139] [140] [141] [142] [143]
# Diagnostic guidelines

## International

**Measurement of blood pressure in humans**  [47]
*Published by:* American Heart Association  *Last published:* 2019

**Resistant hypertension: detection, evaluation, and management**  [59]
*Published by:* American Heart Association  *Last published:* 2018

**Hypertension Canada’s 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children**  [56]
*Published by:* Hypertension Canada  *Last published:* 2018

**2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults**  [5]
*Published by:* American College of Cardiology; American Heart Association  *Last published:* 2018

**High blood pressure in adults: screening**  [46]
*Published by:* US Preventive Services Task Force  *Last published:* 2015

**The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure**  [1]
*Published by:* National Heart, Lung, and Blood Institute  *Last published:* 2004

**2018 ESC/ESH guidelines for the management of arterial hypertension**  [2]
*Published by:* European Society of Cardiology; European Society of Hypertension  *Last published:* 2018

## Treatment guidelines

## International

**Standards of medical care in diabetes - 2019**  [70]
*Published by:* American Diabetes Association  *Last published:* 2019

**Resistant hypertension: detection, evaluation, and management**  [59]
*Published by:* American Heart Association  *Last published:* 2018

**Hypertension Canada’s 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children**  [56]
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<td>2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults</td>
<td>American College of Cardiology; American Heart Association</td>
<td>2017</td>
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<td>Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets</td>
<td>American College of Physicians; American Academy of Family Physicians</td>
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<td>Treatment of hypertension in patients with coronary artery disease</td>
<td>American Heart Association, American College of Cardiology, American Society of Hypertension</td>
<td>2015</td>
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<td>2014 evidence-based guideline for the management of high blood pressure in adults</td>
<td>Eighth Joint National Committee (JNC 8)</td>
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<td>Guidelines for the primary prevention of stroke</td>
<td>American Heart Association; American Stroke Association</td>
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<td>The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure</td>
<td>National Heart, Lung, and Blood Institute</td>
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<td>2018 ESC/ESH guidelines for the management of arterial hypertension</td>
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<td>2018</td>
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Online resources

1. AHA Centers for Health Metrics and Evaluation: 2017 hypertension guidelines visualization (external link)

2. ACC/AHA: corresponding values of systolic blood pressure/diastolic blood pressure for clinic, home blood pressure monitoring, daytime, nighttime, and 24-hour ambulatory blood pressure monitoring measurements (external link)

3. American College of Cardiology: ASCVD risk estimator plus (external link)

4. US and European guidelines - classification and management (external link)
Key articles


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