# 51 - 288 Hypertension

## 288 Hypertension

■ ■FURTHER READING Bhatt DL: Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease. Philadelphia, Elsevier, 2024. Kumar V et al: Transcatheter aortic valve replacement programs: Clin ical outcomes and developments. J Am Heart Assoc 9:120.015921, 2020. Lawton JS et al: 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: A report of the American College of Cardiology/ American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 145:e18, 2022. Paul K. Whelton

Hypertension High blood pressure (BP) is a leading risk factor for cardiovascular disease (CVD), including ischemic and hemorrhagic stroke, coro nary heart disease (CHD), heart failure (HF), peripheral arterial dis ease (PAD), chronic kidney disease (CKD)/end-stage kidney disease (ESKD), dementia, and all-cause mortality. Hypertension, a subset of high BP, is very common no matter how it is defined and results in a huge burden due to death, morbidity, disability, social and workplace disruption, and cost to the individual and society. According to data from the National Ambulatory Medical Care Survey (NAMCS), hyper tension is a component for more than one-third of all visits to officebased physicians by U.S. adults. Likewise, global estimates have ranked hypertension as the most common reason for primary care visits worldwide. Hypertension is often associated with other CVD risk fac tors, resulting in a higher risk of complications and related burden of illness. The optimal approach to high BP is to prevent its development, but diagnosis, treatment, and control of hypertension also provide an effective means to reduce the risk of BP-related CVD. Unfortunately, both strategies are poorly implemented worldwide, resulting in a high burden of preventable disease. BLOOD PRESSURE PHYSIOLOGY AND PATHOPHYSIOLOGY Complex and incompletely understood mechanisms control blood flow in individual organs and the arteriolar system. At the most basic level, arterial BP is controlled by cardiac output and peripheral resis tance (Fig. 288-1). However, arterial pressure is largely thought to be controlled by a renal-volume-endocrine pressure control system, in which the blood volume and total peripheral resistance are manipu lated slowly to adjust arterial BP. Cardiac output is influenced by stroke volume and heart rate, with stroke volume being related to myocardial contraction and the size of the intravascular compartment. Changes in cardiac output play an important role in acute BP responses to stressors. Peripheral vascular resistance is determined by functional and anatomic changes in small arteries and arterioles. The vascular endothelium is composed of a single layer of endothelial cells that constitute the inner cellular lining of arterioles. It serves as a direct contact with circulating blood and regulates exchanges between the bloodstream and surrounding tissues. Endothelial cells control vascular tone and, thereby, blood flow by syn thesizing and releasing relaxing and contracting factors such as nitric oxide; metabolites of arachidonic, lipoxygenase, and cytochrome path ways; peptides, including endothelin; adenosine; purines; and reactive oxygen species; and by generating endothelial enzymes that produce vasoactive hormones such as angiotensin II.

Endothelial dysfunction may play an important role in the initiation or progression of hyper tension and atherosclerosis. A wide variety of systems interplay to keep cardiac output and peripheral resistance in balance, including sodium

Stroke volume Cardiac output Heart rate Arterial blood pressure CHAPTER 288 Vascular structure Peripheral resistance Vascular function FIGURE 288-1 Schematic depiction of factors that influence the control of blood pressure. Hypertension handling, primarily by the kidney, and many neural and hormonal systems that influence peripheral resistance by stimulating vascular constriction (e.g., the sympathetic system and the renin-angiotensinaldosterone system [RAAS]) or inducing vasodilation (e.g., bradykinin system), and by modulating hormones that result in excretion or reten tion of sodium (natriuretic peptides and aldosterone, respectively). Most vascular beds have the capacity to autoregulate blood flow. When peripheral arterial resistance is increased, the autoregulatory systems tend to increase vascular resistance within the vascular bed to maintain constant blood flow. During the 1960s, Arthur Guyton hypothesized that the capacity of the kidney to excrete sodium ulti mately dictates long-term changes in levels of BP. Although the Guyton model has been challenged and alternatives proposed, it has had a profound influence on the understanding of BP regulation. A com monly accepted theory is that initial elevation of BP is due to increased cardiac output and expanded intravascular volume; peripheral resis tance increases and cardiac output reverts toward normal over time. Whether or not this is the typical sequence of events in the pathogen esis of hypertension, salt can activate a number of neural, endocrine, paracrine, and vascular mechanisms that have the potential to increase arterial pressure. As arterial pressure increases in response to a high intake of sodium chloride, urinary sodium excretion increases, and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this “pressure-natriuresis” phenomenon may involve a subtle increase in glomerular filtration rate (GFR), decreased sodium absorption capacity in the renal tubules, and hor monal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pres sure are required to achieve natriuresis and sodium balance. Many of the drugs used to manage high BP work though influ ences on the various BP control mechanisms. For example, direct vasodilators and calcium channel blockers (CCBs) work by induc ing arteriolar vasodilation. Agents that block the RAAS, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin recep tor blockers (ARBs), and renin inhibitors, act by blocking the vaso constricting effects of angiotensin II and sodium-retaining effects of aldosterone. ACEIs also inhibit inactivation of the vasodilator bradyki nin, resulting in angioedema in some patients treated with this agent. Beta blockers tend to affect BP by impairing the action of sympathetic system neurotransmitters that stimulate vasoconstriction and heart rate. For example, beta blockers can antagonize the neurotransmitter acetylcholine as well as epinephrine and norepinephrine. In addition to being the most important site for the effect of agents that block the RAAS activity, many drugs affect electrolyte and fluid exchange in the kidneys. Carbonic anhydrase inhibitors have a diuretic effect in the proximal tubules, but due to side effects and diminishing efficacy over time, they are rarely used for BP control. Thiazide and thiazidelike diuretics work to enhance sodium excretion in the distal convo luted tubule and are a mainstay of drug therapy for BP control. They work by reducing intravascular volume, but over the long term, their effect on BP is through reducing peripheral arteriolar resistance. Loop diuretics are more potent diuretics that produce sodium excretion in the loop of Henle. They tend to be relatively short-acting agents that are better suited for sodium excretion than BP reduction. Mineralo corticoid receptor antagonists (MRAs) or aldosterone antagonists are diuretic drugs that

work in the distal tubule of the kidney, including the distal convoluted tubule, connecting the tubule and cortical collect ing duct, to antagonize the action of aldosterone at mineralocorticoid

receptor sites. These are examples of presumed principal mechanisms of action, but many drugs have other effects on the control of vascular tone and cardiac output that play a role in their effects on BP.

BLOOD PRESSURE MEASUREMENT Commonly, BP measurements are used to estimate an individual's average level of BP; estimate their risk of CVD, in combination with other indicators; and determine the need for hypertension prevention or treatment. Office and clinic BP measurements are among the most common procedures in clinical practice and arguably provide the best assessment of BP because they have been used in almost all of the landmark BP-CVD risk prediction cohort studies and hypertension prevention and treatment trials. The need for standardization of the BP measurement procedure was recognized by early advocates of BP assessment. Subsequently, the effects of factors that can systematically (predictably) result in falsely high or low BP estimates were quanti fied, which formed the basis for BP measurement recommendations by professional societies and clinical practice guideline committees. BP also varies randomly (nonpredictably) within and between visits, resulting in corresponding recommendations to rely on an average of repeated readings obtained at more than one visit for classification of an individual's average level of BP. For many years, U.S. clinical prac tice guidelines have recommended using an average of two or more BP measurements obtained at two or more visits to estimate the usual level of BP. The most important elements for obtaining accurate office BP measurements are visually depicted in Fig. 288-2 and outlined below. PART 6 Disorders of the Cardiovascular System • Instruct the patient to avoid a full bladder and abstain from caffeine, smoking, alcohol, or exercise for 30 min prior to the measurements. • Use a quiet room with a comfortable ambient temperature. • Explain the procedure to the patient, including the number of readings. • Instruct the patient to rest for 3–5 min prior to the first measure ment and avoid talking or distractions such as cell phone use during the rest period and subsequent BP measurements. • Seat the patient in a chair with upright back support. The patient's feet should be flat on the ground and the measurement arm com fortably supported such that the cuff is at heart level. • Use a clinically validated, preferably automated BP measurement device. Choose a cuff that is the correct size for the patient's arm, and measure their BP at the mid-brachial level. • The BP measurements should be obtained by a trained, preferably certified, member of the health care team using the arm with the highest pressure at the first visit. No talking during rest period and between measurements Apply the cuff to bare upper arm, approximately 2–3 cm above the elbow crease Arm bare and resting. Mid-arm at heart level Back supported Feet flat on floor FIGURE 288-2 Schematic depiction of the important elements for accurate measurement of office blood pressure. (Reproduced with permission from AK Cheung et al: International consensus on standardized clinic blood pressure measurement: A call to action. Am J Med 136:438, 2023.)

TABLE 288-1 American College of Cardiology/American Heart Association Blood Pressure Classification System in Adults SYSTOLIC BP, mmHg DIASTOLIC BP, mmHg BP CATEGORY Normal BP <120 and <80 Elevated BP 120–129 and <80 Stage 1 hypertension 130–139 or 80–89 Stage 2 hypertension ≥140 or ≥90 Abbreviation: BP, blood pressure. • Use an average of two or more readings at two or more visits to estimate the patient's usual level of BP. • Provide the patient with the results and an interpretation of their clinical implications. Most clinical practice guidelines

recommend use of a clinically vali dated oscillometric BP measurement device, a method that eliminates several sources of measurement error and does not require periodic recalibration. Several websites provide a listing of BP measurement devices that have been clinically validated to international standards. These include the Validate BP website in the United States (https:// www.validatebp.org/) and the STRIDE BP website in Europe (https:// stridebp.org/bp-monitors). Similarly, many free office and home BP measurement training and certification courses are available, includ ing an easy-to-access course sponsored by the Pan American Health Organization, World Hypertension League, and others (https://campus. paho.org/en/node/29166). DEFINITION OF HYPERTENSION BP classifications systems differ by country and have changed substan tially over time. The current classification proposed by the American College of Cardiology (ACC) and American Heart Association (AHA) for office/clinic BP measurements in U.S. adults is displayed in Table 288-1. Correct classification presumes accurate BP measurement and aver aging of two or more readings obtained at two or more occasions. When the systolic BP (SBP) and diastolic BP (DBP) readings are in different categories of BP, the higher classification should be chosen. In children and adolescents <13 years of age, hypertension is generally based on a comparison with age-, sex-, and height-specific normative data. Hypertension is defined as an average of three SBP or DBP readings at or above the 95th percentile or an SBP or DBP ≥130 or 80 mmHg, respectively. This chapter is focused on BP in adults ≥18 years. Despite the importance and relative simplicity of accurate BP readings, errors in BP measurement are common in routine clinical practice. Generally, SBP is overestimated by an average of ~7 mmHg, which results in a 15–20% overestimation of hypertension prevalence. However, underestimation of BP and failure to diagnose hypertension are also common. Clinical practice errors vary by level of BP and practice settings and are inconsistent over time, making it impos sible to use formulae to correct the errors. For those who aspire to practice evidence-based medicine, the only solu tion is to follow the recommendations for accurate and precise BP measurements that are advocated by the AHA, ACC, and many other organizations. Having a trained non physician staff member obtain routine BP measurements provides an efficient and cost-effective means of obtaining high-quality observations. This is the common practice in research studies and in many large U.S. systems of care. OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENT Office BP measurements provide a limited and potentially biased depiction of an individual’s usual level of BP. Guide lines commonly recommend complementing office BP readings with out-of-office BP measurements to confirm high office readings and to probe for higher or lower BPs

 outside the office. White coat hypertension, in which office BPs meet the criteria for hypertension but out-of-office BPs are nonhypertensive, and masked hypertension, in which office BPs are nonhypertensive but out-of-office BPs meet the criteria for hypertension, are common, with prevalence estimates of 15–25% for both conditions. Adults with white coat hypertension have a CVD risk profile that is more like those with out than those with sustained high BPs in and out of the office and they may be best treated with nonpharmacologic interventions, with careful monitoring to recognize a transition to sustained hypertension. In con trast, adults with masked hypertension have a CVD risk profile that is like those with sustained hypertension and may be better treated with a combination of antihypertensive drugs in addition to nonpharma cologic therapy. Masked hypertension should be suspected especially in adults with an elevated but nonhypertensive office BP and evidence of end-organ damage such as left ventricular hypertrophy

or protein uria. Home BP measurements provide the most practical approach to obtaining out-of-office BP readings and provide the additional benefit of engaging patients in their own care. When home BP measurements are desired, patients should be instructed to use a clinically validated BP measurement device and trained to measure their BPs accurately and precisely using the same approaches outlined for measurement of office BPs. Most guidelines recommend using an average of two to three measurements obtained in the morning (before taking antihyper tensive medications) and evening. In the United States, obtaining home BP measurements for about 3 days prior to an office visit represents a reasonable and practical option for estimating a patient's usual level of home BP. The BP for recognition of hypertension is the same for office and home BP measurements (SBP ≥130 and DBP ≥80 mmHg). Likewise, the BP control is defined as an SBP/DBP <130/80 mmHg in both settings. Many home BP measurement devices allow for storage of the readings on a memory chip and for transfer to the physician's office by use of telemetry. This approach thwarts the potential for the bias of more favorable readings that can occur with written patient self-reports. Ambulatory BP measurements are best obtained by prac titioners with special expertise in this technique and interpretation of the results. The equivalent SBP/DBP readings for an office average of 130/80 mmHg are 130/80, 110/65, and 125/75 mmHg for daytime, nighttime, and 24-h ambulatory readings, respectively. Ambulatory BP measurements provide the potential for scrutiny of nighttime readings, which may provide the best BP prediction of CVD risk. Specifically, those whose BPs fail to follow the usual pattern of a pronounced decre ment during the nighttime (nondippers) tend to have a higher risk of CVD. BP nondipping is more common in non-Hispanic blacks than the other major racial/ethnic groups in the United States. Ambula tory BP measurement is relatively expensive and intrusive. Patients in the United States are usually reluctant to undergo repeat ambulatory BP measurements, making this measurement method most useful in confirming the diagnosis of hypertension, especially where uncertainty is a special concern. Wearable devices, including watches, hold great promise for the provision of convenient ways to obtain a more com prehensive assessment of daytime and nighttime BPs, but none of the currently available options are clinically valid. PREVALENCE OF HYPERTENSION Prevalence estimates vary depending on the criteria for definition of hypertension, the methods for BP measurement, and the population being studied; hypertension is very common, especially at older age. Age-related increases in BP are noted in almost all countries. Gener ally, SBP increases progressively until about the eighth decade of life. DBP also increases with age, but less steeply than SBP, until about the fifth decade of life and remains stable or declines thereafter. Iso lated systolic hypertension is common late in life due to a widening of the pulse pressure (difference between SBP and DBP). Generally, those who have the highest or lowest BPs early in life tend to "track" in the same extremes of BP over life, with high pressures early in life providing a crude opportunity to identify those at higher risk for hypertension in adulthood. Little or no age-related change in BP has been observed in many isolated populations and in subsets of popula tions in countries where age-related increases in BP are common. This observation indicates that there is no biological necessity for the com monly observed age-related increase in BP and underscores the value of interventions aimed at prevention of hypertension. Migrant studies that have tracked isolated populations from their native environment to nonnative settings have uniformly reported progression to the more common pattern of age-related increases in BP. These BP changes have been associated with increases in dietary sodium and decreases in potassium intake, consumption of a less healthy diet, decreased physi cal activity, increases in body weight, and increased intake of alcohol. Based on the ACC/AHA criteria for diagnosis, >103 million adults in the United States have hypertension, making it one of the most com mon health conditions reported. Hypertension is

present in ~20–30% of U.S. adults aged 20–44 years, but the prevalence increases to 80–85% in those aged 75 years or older. The overall prevalence of hyperten sion in U.S. adults has remained fairly stable in recent decades (~46% overall). Men have slightly higher BPs compared to women during the first half of life, but the opposite is true in later life. In the United States, non-Hispanic black adults have a prevalence of hypertension (59%) that is substantially higher compared to whites (45%), Hispanics (47%), or Asians (46%). Adjusted estimates of hypertension in adult non-Hispanic black men and women are reported to be 59 and 56%, respectively, whereas the corresponding estimates for non-Hispanic white men and women are 47 and 41%, respectively. In addition, hypertension in non-Hispanic black adults tends to begin at a younger age and result in more CVD and kidney complications compared to the other major racial/ethnic groups in the United States. The prevalence of hypertension and CVD complications (especially stroke) is higher in the southeastern United States compared to other regions of the coun try, especially the northwest. No matter how defined, hypertension is very common in all parts of the world, with a progressively increasing prevalence in low- and middle-income countries and a slight decline in high-income countries. Using the hypertension definition of SBP ≥140 mmHg, DBP ≥90 mmHg, or taking antihypertensive medication, the prevalence in adults was estimated to be 31.5% (1.04 billion) in low- and middle-income countries and 28.5% (349 million) in high-income countries in 2010. As in the United States, hypertension prevalence is very age-dependent and varies by region, race/ethnicity, and other fac tors, including importantly socioeconomic factors, in most countries. LABORATORY AND OTHER INVESTIGATIONS In patients with newly diagnosed hypertension, basic laboratory test ing is indicated to (1) recognize the presence and extent of target organ damage; (2) facilitate the identification of secondary causes of hypertension, including kidney disease and primary aldosteronism; (3) recognize comorbid conditions, including diabetes mellitus and hyperlipidemia; (4) estimate atherosclerotic CVD (ASCVD) risk in patients without a history of a CVD; and (5) assist in the optimal choice of antihypertensive drug therapy. At a minimum, a complete blood count, serum electrolytes (sodium, potassium, calcium), serum creati nine and estimated GFR (eGFR), lipid profile, glycemic status (hemo globin A1c or fasting blood glucose), thyroid-stimulating hormone level, urinalysis and urine albumin-to-creatinine ratio, and 12-lead electrocardiogram (ECG) should be obtained. These basic tests can be complemented by other evaluations as clinically indicated. In some countries, it is not possible to obtain the minimally recommended laboratory results. Guidelines written for clinicians in such countries, including the 2021 World Health Organization (WHO) guideline for the treatment of hypertension in adults, recommend that this should not be an impediment to BP reduction. ESTIMATION OF CARDIOVASCULAR DISEASE RISK Abundant studies have shown that BP is associated with CVD risk in a continuous, progressive, log-linear fashion from low to high levels of SBP and DBP. For SBP, the risk relationship has been documented from as low as 90 mmHg to more than 180 mmHg, suggesting rela tively low levels of BP, if physiological, may be optimal to prevent the genesis of BP-related atherosclerotic complications. It also suggests that

one might reasonably expect a “lower BP is better” finding in antihy pertensive randomized controlled treatment (RCT) trials. In addition to CVD, the level of BP is strongly associated with other diseases, including CKD, ESKD, and dementia. The BP-CVD risk association in observational studies is equally true for men and women. The BPrelated slope for relative risk of CVD is steeper at younger age when BP elevation is often an isolated risk predictor. In older adults, the corresponding slope for CVD risk is less steep, but the absolute risk of CVD is far higher because other CVD risk factors are common in those with an elevated BP. At any level of BP, the risk of a

CVD complication varies dramatically with more than a 30-fold difference in 10-year predicted risk of CVD for those with an isolated elevation of BP compared to their counterparts with multiple CVD risk factors in addition to an elevated BP. This observation has special relevance for clinical decision-making in patients with a usual SBP between 130 and 139 mmHg. In individuals with stage 1 hypertension as an isolated CVD risk factor, the 5- or 10-year risk of a CVD event may be quite small and limit enthusiasm for introducing antihypertensive drug therapy. However, when stage 1 hypertension is accompanied by other CVD risk factors, the corresponding risk of ASCVD may be quite high and make prescription of antihypertensive drug therapy much more appealing. In antihypertensive clinical trials, the relative risk reductions for CVD events are similar in groups with different levels of underlying CVD risk, but the absolute benefit is much greater in the groups at higher risk for ASCVD. For both these reasons, CVD risk assessment should be part of the initial evaluation.

PART 6 Disorders of the Cardiovascular System Patients with a history of a prior CVD complication are known to be at high risk for recurrent CVD events. In those without a history of prior CVD, ASCVD risk should be estimated using a risk calculator. For U.S. adults 40–75 years of age, use of the ACC/AHA pooled cohort equations estimator is recommended because it has been validated in non-Hispanic white and black adults. Those with a 10-year risk of ASCVD ≥10% should be considered at high risk. PREVENT is an updated risk predicting model that is based on a larger and more cur rent dataset than that used for the pooled cohort equations model. It incorporates an assessment of kidney (glomerular) function and allows for inclusion of urinary albumin/creatinine ratio, zip code for assess ment of the social determinants of health, and hemoglobin A1c where indicated and has been introduced by the AHA as a replacement for the pooled cohort equations. It can be used in U.S. adults aged 30–70 years to predict 10- and 30-year CVD risk. It includes the prediction of heart failure risk, an important feature in the care of patients with hyperten sion. Over time, the PREVENT instrument is expected to replace the current pooled cohort equations risk prediction model. CAUSES OF HYPERTENSION ■ ■PRIMARY HYPERTENSION Most adults have “primary” hypertension, with no obvious underlying anatomic cause of their high BP. Adoption, twin, clinical, and family studies provide evidence for a heritable component of high BP and hypertension. However, much of this may be due to a shared environ ment because, with rare exceptions, genetic investigations have only identified modest polygenic associations between multiple genes and BP. While genetic research remains an important area for investigation, the clinical implications of genetic studies for diagnosis and manage ment of high BP are currently very limited. Strong associations with level of BP have been reported for several general environmental exposures, including heavy metals such as lead, mercury, cadmium, and arsenic. Several indicators of air pollu tion, commonly including levels of particulate matter with a diam eter of 2.5 microns (PM2.5) or less, have been associated with higher levels of SBP and DBP. In most studies, the increase in SBP has been ~3–5 mmHg, but the magnitude can vary depending on quantity and duration of the exposure. Air pollution is a challenge worldwide, but the level of exposure to pollutants varies widely by geography, climate, season, and extent of economic development. In addition to air pollution, clinically important changes in BP are recognized in geographic regions that experience large seasonal variations in ambient

temperature, with lower and higher BPs during the warmest and cold est seasons, respectively. BP also tends to be higher in those who are acutely exposed to high altitudes, possibly due to a combination of hypoxia and cold temperatures. Personal environmental exposures related to

components of diet, physical activity, and alcohol consumption seem to be responsible for much of the age-related increases in BP that are common in most countries. A large body of ecological, migrant, and longitudinal cohort studies have documented higher BPs in those who consume unhealthy diets, have an excessive intake of sodium or an inadequate intake of potassium, are physically inactive, are overweight or obese, or consume alcohol. Many of these exposures have also been linked to CVD com plications. For example, insufficient dietary intake of potassium has been identified as a risk factor for stroke in many studies. Stress and other psychosocial indicators have also been associated with higher BPs and CVD events. The six personal exposures identified in Table 288-2 (diet quality, body weight, excessive dietary sodium intake, insufficient dietary potassium intake, physical inactivity, and alcohol consumption) are all highly prevalent and strongly associated with higher BP and age-related increases in BP. About half of U.S. adults report attempts to eat a heart healthy diet, but this is likely to represent an overestimate. Almost all adults worldwide exceed the intake of dietary sodium and fail to meet the level of dietary potassium recommended by the WHO and national organizations. Likewise, excess body weight is very com mon in many countries. For example, approximately three-quarters of U.S. adults are either overweight (body mass index [BMI] 25–29 kg/m2) or obese (BMI ≥30 kg/m2). More than a quarter of U.S. adults report no physical activity outside their workplace, and about half report less than the recommended level of physical activity (≥150 min of aero bic exercise/week). About 85% of U.S. adults report consumption of alcohol at some point during their life, with >60% reporting alcohol consumption during the previous year and 25% reporting binge drink ing during the previous month. Thus, these six exposures are not only closely related to level of BP and targets for interventions aimed at BP lowering but also extremely common exposures. ■ ■SECONDARY HYPERTENSION A minority of patients have “secondary” hypertension, with an overt underlying anatomic or biochemical cause for their high BP. Second ary hypertension should be considered during the evaluation of all patients with new-onset hypertension and in selected patients with prevalent hypertension who have indicators that suggest the possibil ity of a complicating secondary cause of hypertension, including (1) treatment-resistant hypertension; (2) abrupt worsening of hyperten sion; (3) disproportionate target organ damage for level of BP; and (4) laboratory or diagnostic findings such as unprovoked hypokalemia, proteinuria, or left ventricular hypertrophy. The approximate preva lence, pathophysiology, possible clinical and physical examination findings, common screening and confirmatory tests, and potential treatments for the six most common causes of secondary hypertension are summarized in Table 288-3. Obstructive Sleep Apnea Obstructive sleep apnea (OSA) is probably the most common cause of secondary hypertension. It is closely associated with overweight, obesity, and other comorbidities. The reported prevalence of OSA varies substantially depending on the criteria used for definition and methods of ascertainment. However, it is very common and may be present in as many as 15–30% of adult men and 10–15% of adult women in the United States. More than half of U.S. adults with OSA have hypertension and >30% of U.S. adults with hypertension have OSA. OSA and hypertension share many common pathophysiologic features, including being overweight, obe sity, unhealthy lifestyles, and abnormalities of the renin-angiotensin system and fluid distribution. Sympathetic system activation due to intermittent hypoxia is also an important component of the underly ing pathophysiology in OSA. Almost three-quarters of patients with OSA are overweight or obese. In general, there is a direct association between the severity of OSA and an individual’s level of BP as well as their resistance to antihypertensive therapy. Resistant hypertension,

TABLE 288-2 Summary Information for the Six Best Proven Nonpharmacologic Interventions That Lower Blood Pressure CHARACTERISTIC BP ASSOCIATION INTERVENTION REGIMEN EXPECTED CHANGE IN BP Diet BPs are lower in those who consume heart-healthy diets. Consumption of a hearthealthy diet, especially the Dietary Approaches to Stop Hypertension (DASH) diet. Body weight Increased body weight is directly associated with SBP/ DBP. Almost 75% of U.S. adults are overweight (BMI 25–<30 kg/ m2; 31%) or obese (BMI ≥30 kg/ m2; 42%). In most patients, weight loss should be achieved by behavioral counseling. In a minority, drug therapy should be considered. Bariatric surgery should be confined to adults with a BMI ≥40 kg/m2 or ≥35 kg/m2 and hypertension or another obesityrelated comorbidity. Sodium intake Dietary sodium is directly associated with SBP, and excessive intake may be important in age-related increases in BP. Behavioral counseling, use of salt substitutes, public health messaging, and policy to reduce the amount of sodium added during food processing and commercial preparation. Potassium intake Potassium intake is inversely associated with BP and a lower risk of CVD, especially stroke. Dietary or pill supplementation, but the former is preferred. An additional intake of 2000 mg/d (~50 mmol/d). Physical activity Observational studies identify a strong inverse association between physical activity and BP, hypertension, and CVD. Aerobic, dynamic resistance, and isometric resistance exercises. Alcohol consumption Alcohol intake is associated with BP and hypertension in a direct and roughly linear fashion, with no threshold for the association. Most commonly, substitution of lower alcoholic or nonalcoholic beverages, but behavioral counseling and abstinence, without access to alcohol, have been used in some trials. Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; RCT, randomized controlled trials; SBP, systolic BP. snoring, poor quality sleep, breathing pauses during sleep, and day time sleepiness are common clinical indicators of OSA. Several simple questionnaire-based tests are available to screen for those who should be evaluated more carefully with a sleep study (polysomnography). Lifestyle improvements, especially those resulting in weight loss, are an important component of treatment for both OSA and any associated hypertension. OSA-specific treatment includes continuous positive airway pressure (CPAP), but meta-analyses demonstrate limited BP lowering due to CPAP treatment. As a result, hypertension in patients with OSA should be treated with antihypertensive drug therapy in addition to nonpharmacologic therapy. Medication and Other Substances Prescription and over-thecounter medications, herbal and food additives, and illegal substances are often identified as secondary causes of new-onset hypertension or diminished BP control in patients being treated for hypertension. Typically, the increase in BP results from a direct pressor effect of the agents, but these exposures can also have an indirect effect on

DASH diet meal plans are readily available. With good adherence to the DASH diet plan, an average SBP reduction of about 5 mmHg can be expected in patients with and 2–3 mmHg in those without hypertension. CHAPTER 288 Behavioral interventions are aimed at a combination of calorie reduction and increased physical activity. Generally, SBP is reduced by ~1 mmHg for every kilogram reduction in body weight. In high-quality RCTs, an average reduction of about 10 lb (4.5 kg) has been common at 6–12 months. Hypertension The sodium-BP dose response is almost linear, so any reduction in sodium intake is beneficial. Optimal target recommendations vary from <1500 to 2300 mg sodium intake per day. In high-quality behavior change trials, average sodium intake is reduced by ~25% and SBP by ~5 mmHg and 2–3 mmHg for adults with and without hypertension, respectively. Use of salt substitutes has resulted in prevention of stroke (14%), CVD (13%), and allcause mortality (12%) in addition to BP lowering. The recommended intake of

potassium in adults is ~3500 mg/d. A dose-response meta-analysis suggests supplementing usual intake by ~1200 mg/d may be optimal. Potassium supplementation is contraindicated in patients with hyperkalemia or advanced kidney disease or who are taking medicines that increase the risk of hyperkalemia. Clinical trial meta-analyses have repeatedly shown that potassium supplementation by diet or pill use lowers BP. The average reduction in SBP has been ~5 and 3 mmHg in adults with and without hypertension, respectively. Greater reductions are observed in adult black patients and those consuming large amounts of dietary sodium. Most trials have evaluated aerobic exercise interventions, and this type of exercise is commonly prescribed. Most guidelines recommend ≥150 min of aerobic exercise per week. However, any increase in physical activity and any type of exercise are likely to be be beneficial. In adults with hypertension, aerobic exercise is likely to reduce SBP by ~5 mmHg and, when combined with dynamic resistance exercise, by ~7 mmHg. The extent of BP lowering depends on the starting level of BP and success of the intervention. Most interventions have targeted a reduction in alcohol consumption, often to ≤2 and ≤1 standard drinks per day in men and women, respectively. However, any reduction in alcohol consumption is helpful. The extent of BP lowering depends on the starting level of alcohol consumption and the magnitude of the reduction in alcohol intake. Commonly, alcohol reduction trials have resulted in an SBP reduction of >5 mmHg in adults with hypertension. BP as a result of drug-drug or drug-nondrug exposure interactions. Some of the most common prescription drugs that can increase BP include amphetamines, angiogenesis inhibitors, antidepressants and antipsychotic agents, decongestants, oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic corticosteroids. Examples of illicit drugs that can result in a higher BP include cocaine, marijuana, amphetamines, and methylenedioxymethamphetamine. Herbal treatments that have been reported to raise BP include arnica, ephedra (Ma-Huang), ginseng, guarana, consumption of large quanti ties of licorice, and St. John’s wort. Finally, caffeine and several anes thetic agents can result in short-term elevation of BP. A careful history will identify most of these agents and will allow for use of alternatives or a reduced dosage in most patients. The exact prevalence of expo sure to any of these agents is uncertain but high. For example, in the nationally representative 1999–2004 National Health and Nutrition Examination Survey (NHANES), >26% of U.S. adults reported regular NSAID use, and the percentage was much higher in older adults and in non-Hispanic whites.

Continuous positive airway pressure alternative therapy, or maintenance Management of the specific kidney (CPAP) treatment for OSA has little aimed at weight loss, is indicated (sleep study) Lifestyle improvement, especially Treatment of ASCVD risk factors, Adrenalectomy (laparoscopic or of exposure but management of History taking History taking Discontinuation, substitution of Antihypertensive drug therapy. for both OSA and associated including hypertension. PART 6 Disorders of the Cardiovascular System disease, if feasible. hypertension. TESTS TREATMENT effect on BP. high BP. sonography, CT, or MRI Saline suppression Polysomnography CAUSE PREVALENCE PATHOPHYSIOLOGY CLINICAL INDICATORS PHYSICAL EXAMINATION SCREENING TESTS CONFIRMATORY Renal biopsy Imaging by albuminuria, glucose (several have been edema, report of hematuria Proteinuria, renal mass Serum creatinine, airway narrowing OSA screening questionnaires clinical examination High plasma abnormality validated) Obesity and signs of upper physical exam findings, No specific findings on by medical history report Occasionally, specific e.g., signs suggesting cocaine use Resistant hypertension, snoring, Severe or resistant hypertension Resistant hypertension, fatigue, Varies depending on exposure. Usually exposure best detected pauses during sleep, daytime poor quality sleep, breathing sleepiness, overweight and TABLE 288-

3 Summary Description of the Most Common Secondary Causes of Hypertension obesity Various kidney diseases, including polycystic renal disease, chronic many common pathophysiologic glomerulonephritis, diabetic and features, including overweight hypertensive kidney disease, OSA and hypertension share recurrent stones, and kidney the sympathetic system due important component of the to intermittent hypoxia is an Idiopathic bilateral adrenal and obesity. Activation of pathophysiology for OSA. infections. One of the most common hypertension, and ~30% adults reporting regular (10–30% of U.S. adults). with hypertension have More than 50% of U.S. exposures. For NSAID adults with OSA have causes of secondary OSA is very common Numerous potential hypertension (>5%). alone, >26% of U.S. High prevalence. aldosteronism One of the more OSA. use. parenchymal sleep apnea Obstructive Medication substances and other Primary disease. Renal (OSA)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CT, computed tomography; MRI, magnetic preferred in patients with ASCVD and those with very diffuse fibromuscular with inclusion of a mineralocorticoid and ARBs should not be used. Initial safety record and known efficacy in with discrete fibromuscular disease antihypertensive medication. ACEIs hyperplasia best treated medically, surgical) for many patients with an or the CCB nifedipine is commonly use of the β-blocker labetalol and/ changes to reduce sodium intake receptor antagonist, and lifestyle improve hypertension in patients recommended because of their angiography PTA may cure or substantially lesions. Medical treatment is Hypertension due to adrenal Lifestyle counseling and adrenal adenoma. and body weight. pregnancy. disease. measured BP readings recognition of high BP, generally accepted as the gold standard test. taken on ≥2 occasions based on an average aldosterone levels is helpful, but adrenal Digital subtraction challenge test are vein sampling for of ≥2 accurately test or captopril screening tests Diagnosis by ratio, when measured magnetic resonance, under standardized CT of the abdomen aldosterone/renin or CT angiography options, including ultrasonography, Various imaging proteinuria No specific conditions Doppler High BP, with or without abdominal renal artery Bruits, especially bruit Early, abrupt-onset hypertension (consider fibromuscular disease) accompanied by proteinuria or other evidence of target organ Rapidly worsening or resistant Family history of early-onset Incidental finding of adrenal Nonspecific fatigue, muscle hypertension in older adults Preeclampsia if high BP is Obstructive sleep apnea resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PTA, percutaneous transluminal angioplasty. hypertension or stroke cramps, or weakness (consider ASCVD) Hypokalemia adenoma damage High BP from reduced placental perfusion approximate 5%. Usually unilateral disease due to usually disappears after delivery. ASCVD (90%) with >70% arterial About 10% due to fibromuscular disease, typically occurring in Varies depending on whether hypertension seems to result onset or chronic. New-onset peripheral resistance, which and subsequent elevation in middle-aged white women. Rarely due to other causes Benign adrenal adenoma the hypertension is new hyperplasia (60–70%) Occasionally, familial lumen narrowing. (30–40%) secondary hypertension, approximate prevalence BP in ~5% of adults with responsible for the high preeclampsia 3%, and disease Generally reported to of hypertension 10%, eclampsia 0.1–0.3%. common causes of During pregnancy, hypertension. Renovascular Hypertensive disorders of pregnancy

Hypertension

CHAPTER 288 Renal Parenchymal Disease This is also relatively common and probably accounts for >5% of all non-OSA and medication-related secondary causes of hypertension. It can result from almost any type of underlying kidney disease but is somewhat more common with glomerular than interstitial disorders. Most patients with CKD dis ease have hypertension. Importantly, it is often difficult to determine the extent to which a patient's high BP is the cause or a consequence of their kidney disease. Activation of the RAAS is often a part of the underlying pathophysiology that leads to hypertension. Clinical indicators of hypertension due to renal parenchymal disease include treatment resistance, fatigue, palpation of a renal mass, hematuria, pro teinuria, elevated creatinine, or hyperglycemia. Imaging with sonog raphy, computed tomography (CT), or magnetic resonance imaging (MRI) can be helpful for the diagnosis of some forms of underlying kidney disease. Renal biopsy is most helpful when glomerulonephritis is suspected. Most patients with CKD have a variety of both conven tional and novel risk factors for ASCVD placing them at high risk for CVD complications. Improvement of CVD risk factors, including hypertension, is an essential element of treating patients with CKD. Often, control of hypertension may require use of three or more anti hypertensive agents in addition to lifestyle management. Diuretics and RAAS inhibitors such as ACEIs and ARBs are obvious components of the antihypertensive drug treatment regimen. Traditionally, thiazide and thiazide-like diuretics were thought to be relatively ineffective for the management of patients with a serum creatinine >3 mg/dL, but a recent well-conducted trial documented substantial BP and albu minuria reduction in patients with advanced CKD who were treated with the long-acting diuretic chlorthalidone. Finerenone, a newer MRA, has also been shown to enhance BP reduction in patients with advanced CKD. Gliflozins or sodium-glucose cotransporter 2 (SGLT2 inhibitors), which are often very useful in the management of patients with CKD, are diuretics and may provide a small reduction in BP. If possible, the underlying kidney disease should be treated with specific therapy. Primary Aldosteronism A relatively common cause of secondary hypertension, primary aldosteronism may be the underlying cause of high BP in ~5% of adults with non-OSA and medication-related sec ondary hypertension. However, the reported prevalence varies widely depending on the criteria for diagnosis and the population studied. Most patients with primary aldosteronism (60–70%) have idiopathic bilateral adrenal hyperplasia but ~30–40% have a benign adenoma, usually unilateral. Often, the clinical presentation is subtle with no more than resistant hypertension or nonspecific symptoms. However, in some patients with more pronounced aldosteronism, unprovoked hypokalemia or hypokalemia-related cardiac arrhythmias, such as atrial fibrillation, may be present. Common screening tests for pri mary aldosteronism include abdominal imaging by CT to detect an adenoma and measurement, under standardized conditions, of a high aldosterone/renin ratio in conjunction with high plasma aldosterone levels. Several noninvasive investigations, including the saline suppres sion and captopril challenge tests, can provide more definitive evidence of primary aldosteronism, but adrenal vein aldosterone sampling is generally accepted as the gold standard test for diagnosis. The most important goal is to recognize the minority of patients with a benign unilateral adenoma whose hypertension can be cured or substantially improved by adrenalectomy. The latter can be accomplished by mini mally invasive laparoscopy or by use of traditional surgical techniques. Medical management of hypertension in patients with aldosteronism should include the use of MRA agents. In most patients, spirono lactone is well tolerated but occasionally adverse effects, including hyperkalemia, breast tenderness, or gynecomastia in men, require the substitution of newer, more expensive, alternative MRAs. The screen ing tests and especially the more definitive diagnostic tests for primary aldosteronism require careful attention to detail and are generally best conducted by those who have specialized experience in the evaluation of patients who may have primary

aldosteronism. Likewise, most adre nal adenomas are very small, and removal by laparoscopy or surgery is most successful when performed by an experienced treatment team. Rarely, primary aldosteronism can be caused by an adrenal carcinoma, ectopic malignancy, or rare genetic disorders. Renovascular Hypertension Renovascular obstructions that result in substantial and hemodynamically important occlusion of the renal artery can result in hypertension and impaired renal function. Renovascular disease is found in as many as 25% of patients at autopsy, but renovascular hypertension only accounts for ~1% of the high BP in all patients with hypertension. In ~90% of patients with renovascular hypertension, renal artery obstruction is caused by atherosclerosis. Commonly, atherosclerotic renovascular disease is unilateral and the principal obstruction tends to present as a discrete lesion found close to the origin of the renal artery. Patients with atherosclerotic renovascular disease tend to be older and have other indications of ASCVD, including an abnormal risk factor profile and atherothrom botic lesions in other vascular beds. At times, a bruit can be heard over the renal artery or over the carotid or femoral arteries. A minority of patients with renovascular disease have fibromuscular disease. They tend to be younger, mostly white, women. Their renal artery lesions are more diffuse, with an irregular sawtooth appearance, and they are frequently located in more distal parts of the renal artery compared with atherosclerotic lesions. In addition, bilateral real artery disease is more common in patients with fibromuscular disease than is the case for renovascular disease due to ASCVD. Fibromuscular disease should be suspected in any patient with abrupt-onset hypertension, especially in young white women, and in those with resistant hypertension, or recent worsening of hypertension. Underlying atherosclerosis should be suspected in older patients with other indications of ASCVD and in those with otherwise unexplained worsening of kidney function. The threshold for additional diagnostic investigations should be lower when fibromuscular disease is suspected. A variety of screening tests, including renal ultrasound studies, CT and magnetic resonance angiography imaging studies, renograms, and standardized measurement of plasma renin activity, can be used to exclude other causes of hypertension and to screen for evidence of renovascular disease. Renal angiography provides more definitive evidence of the extent and type of renovascular disease and is cur rently considered to be the gold standard diagnostic test. Skilled inter ventional radiologists can employ digital subtraction angiography to generate high-quality studies with less contrast exposure compared to standard angiography. Hypertension due to renovascular disease is more likely in patients with lesions that occlude >70% of the ves sel lumen. For many years, renal venous renin sampling was a gold standard diagnostic test but is now rarely performed due to a high frequency of false-positive and false-negative results. In many patients with hypertension due to fibromuscular disease, percutaneous transluminal angioplasty results in a cure for their hyper tension or substantially improves the control of their high BP. For this reason, the most important goal in evaluating patients with suspected renovascular hypertension is to recognize individuals with underlying fibromuscular disease. As is the case for some other forms of second ary hypertension, screening, diagnosis, and treatment results tend to be better when conducted by teams with experience in caring for patients with renovascular disease. Several well-conducted random ized controlled trials, with relatively large sample sizes, have failed to demonstrate any special benefit for BP control or renal preservation following percutaneous transluminal angioplasty or renovascular sur gery compared to medical care in patients with atherosclerotic reno vascular hypertension. Most patients with suspected atherosclerotic renovascular hypertension should be managed using a combination of nonpharmacologic and antihypertensive drug therapy, including the use of agents that block the RAAS. In rare instances, arteritis and other inflammatory disease can be the underlying cause of renovascular hypertension.

The underlying cause should be treated in addition to medical management of hypertension. Hypertensive Disorders of Pregnancy Hypertension occurs in >10% of pregnancies in the United States and about 3–5% are complicated by preeclampsia, in which hypertension is accompanied by proteinuria or other evidence of target organ damage. The HELLP

syndrome, in which hypertension is accompanied by hemolysis, elevated liver enzymes, and low platelets, represents a more severe form of preeclampsia. Progression to eclampsia, with seizures as the cardinal feature, occurs in <1% of women with mild and about 3% of those with severe preeclampsia. Hypertension during pregnancy is associated with a higher rate of fetal complications and of hyperten sion and CVD complications for the mother later in life. Hypertensive disorders of pregnancy include the following: (1) chronic hypertension, in which the high BP proceeds pregnancy; (2) gestational hyperten sion, in which new-onset hypertension is recognized after 20 weeks of gestation; (3) preeclampsia potentially culminating in eclampsia; and (4) chronic hypertension with superimposed preeclampsia. Manage ment of hypertension in pregnancy often includes bed rest, nonphar macological interventions, and pharmacotherapy. Clinical trials and meta-analyses provide strong evidence that antihypertensive therapy during pregnancy reduces the risk of progression to more severe hypertension, compared to placebo, but less convincing evidence for prevention of preeclampsia and other fetal complications. ACEI and ARB therapy should be avoided due to the potential for teratogenic side effects. Few high-quality studies have compared the benefits and risks of treatment with other commonly used antihypertensive drugs during pregnancy. Usually, treatment with the beta blocker labetalol, the CCB nifedipine, or the centrally acting α2-adrenergic agonist methyldopa is recommended as providing safe first-line antihypertensive drug therapy, with one trial suggesting that labetalol and nifedipine may be superior to methyldopa for prevention of preeclampsia. A review of prescribing habits in the United States identified labetalol, nifedipine, and the direct vasodilator hydralazine as the three most commonly used antihypertensive agents during pregnancy. Clinical trials have failed to demonstrate a benefit for more intensive therapy to a SBP/ DBP <130/80 mmHg compared to <140/90 mmHg.

PART 6 Disorders of the Cardiovascular System Less Common Causes of Secondary Hypertension There are many other secondary causes of hypertension, but they tend to be infrequent and are generally best considered when patients are referred to consultants with expertise in recognizing rare causes of second ary hypertension. These include Cushing’s syndrome in which large amounts of cortisol are produced in response to excessive levels of adrenocorticotropic hormone (ACTH) produced by a pituitary gland adenoma or ectopic ACTH-producing tumor, an adrenal adenoma, or treatment with glucocorticoids. Clinical signs of note include weight gain in the face (moon face) and trunk, a fatty lump between the shoulders (buffalo hump), thin arms and legs, pink or purple stretch marks on the stomach, hips, thighs, breasts, and underarms, easy bruising, slow healing, and acne. Screening and diagnosis are usually based on an assessment of 24-h urinary corticosteroid levels, imag ing tests, and an overnight dexamethasone-suppression test. More than 75% of patients with Cushing’s syndrome have hypertension. Treatment depends on the underlying cause of the syndrome. Pheo chromocytoma is another rare form of secondary hypertension and is caused by excessive production of catecholamines, usually due to a benign neuroendocrine tumor composed of chromaffin cells located in the adrenal medulla (80–85%) or in extra-adrenal paraganglion tis sue (paraganglioma). Most patients with pheochromocytoma present with hypertension at a relatively young age (often 30–50 years). Many have nonspecific signs and

symptoms, but some have paroxysmal attacks characterized by high BP, sweating, headaches, and cardiac arrhythmias. Screening and diagnosis are usually based on blood and 24-h urinary catecholamine values and abdominal CT, MRI, or positron emission tomography imaging studies. Typically, pheochro mocytomas are treated by complete or partial adrenalectomy using minimally invasive surgical techniques. A small minority of patients with pheochromocytoma have an inherited genetic predisposition such as multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Landau disease, neurofibromatosis, and hereditary paraganglioma syndromes. Coarctation of the aorta is the most common congenital cause of hypertension and results from a birth defect in which a portion of the aorta is narrower than usual. When the defect is severe, the coarctation is likely to be detected early in life and may be associated with other

congenital abnormalities. When the defect is mild, the disorder may not be recognized until early adulthood. The classical physical exami nation findings are delayed and diminished femoral and distal pulses. A systolic mummer may be heard in the posterior intrascapular area, and signs of left ventricular hypertrophy may be detected. Screening and diagnostic tests include imaging studies such as echocardiography, CT, and angiography. Treatment options include balloon angioplasty, surgery, and medical management. Other rare causes of hypertension include hyper- and hypothyroidism, acromegaly, and hypercalcemia. PREVENTION AND TREATMENT OF PRIMARY HYPERTENSION Both nonpharmacologic interventions, mostly lifestyle improvements, and antihypertensive medication play a role in the management of high BP. The overall approach to prevention and treatment of hypertension, which is depicted in Fig. 288-3, is to encourage a healthy lifestyle in adults with a normal BP (SBP/DBP <120/80 mmHg) and actively advise nonpharmacologic therapy in adults with an elevated BP (SBP 120–129 mmHg and DBP <80 mmHg). Adults with stage 2 hyperten sion (SBP ≥140 mmHg or DBP ≥90 mmHg) should be treated with a combination of nonpharmacologic and antihypertensive drug therapy. Most adults with stage 1 hypertension (SBP 130–139 mmHg or DBP 80–89 mmHg) should be managed by active application of nonphar macologic interventions, but in the minority (~30% in the United States) who have a history of CVD or are at high risk for ASCVD, anti hypertensive medication should be added to the nondrug approaches to lower BP. In RCTs, low-dose pharmacotherapy has been effective for BP lowering, prevention of hypertension, regression of left ventricular mass, and prevention of left ventricular hypertrophy in nonhyper tensive patients. However, drug therapy is not recommended for this purpose in any major clinical practice guideline. The next two sections provide a more detailed guide to the selection and application of non pharmacologic and antihypertensive drug treatments. ■ ■NONPHARMACOLOGICAL INTERVENTIONS TO PREVENT AND TREAT HYPERTENSION Many nondrug interventions have been reported to lower BP. Most of them are based on changing personal exposures associated with higher BP. The best proven approaches to nonpharmacologic lowering of BP are displayed in Table 288-2. Generally, the nonpharmacologic interventions used in clinical practice settings require a change in behavior. However, pill supple mentation to enhance potassium intake, renal denervation therapy in selected patients with resistant hypertension, and baroreceptor activa tion therapy are examples of nonpharmacologic treatments that are not primarily based on achieving behavior change. For the nonphar macologic interventions based on behavior modification, the difficulty of achieving the desired changes varies by intervention and patient, but generally, behavior change can be hard to achieve and maintain over long periods of time. Behavior change interventions are most suc cessful when patients accept the need for change, pledge to embrace the behavioral changes that are necessary, and can be counseled by a member of the health care team who is knowledgeable in the tech niques

for behavior change. For weight loss, abstinence from alcohol, physical activity, and high-quality counseling programs that are avail able in convenient locations close to a patient’s home or workplace may provide an alternative option to office/clinic-based counseling. Behavior change can be successful in any patient but is especially likely in those with or at high risk for CVD and in patients who have the time, resources, and desire to concentrate on improving their health behav iors. Not surprisingly, older adults and those with higher socioeco nomic status (SES) tend to be more successful than their younger and lower SES counterparts. The following are brief summaries of specific aspects of the six interventions identified in Table 288-2. Diet Quality Heart healthy diets tend to lower BP and improve other diet-related CVD risk factors, such as low-density lipoprotein cholesterol and blood glucose. For example, a reduction in BP has

Recommendations for management by category of blood pressure SBP/DBP <120/80 mmHg (Normal BP) SBP 120–129/DBP <80 mmHg (Elevated BP) SBP 130–139 or DBP 80–89 mmHg (Stage 1 Hypertension) Not at high risk No prior CVD, or No CVD and not at high risk

- using risk calculator Encourage healthy lifestyle habits (Table 288-2) Active application of nonpharmacologic therapy (Table 288-2) Reassess after 3–6 months Reassess after 1 month Reassess after 12 months FIGURE 288-3 Recommendations for nonpharmacologic and antihypertensive drug therapy by category of blood pressure. ASCVD, atherosclerotic CVD; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; HTN, hypertension; SBP, systolic BP. been a consistent finding in trials that have evaluated the Mediter ranean diet, low-carbohydrate diets, and vegetarian and vegan diets. The DASH (Dietary Approaches to Stop Hypertension) diet is a heart-healthy diet that was specifically formulated to lower BP. The DASH diet is high in vegetables, fruits, whole grains, and low-fat dairy products and low in fats, saturated fats, and cholesterol. It has been extensively evaluated, and many DASH resources and support systems are readily available to health care providers and the public. For these reasons, it is commonly recommended as the best heart-healthy diet choice for BP reduction. Many of the DASH evaluation trials have been conducted as feeding studies in which patients are given specially prepared foods as a replacement for their usual diet. Compared to trials based on behavior change, feeding studies require less effort by the patient, achieve greater intervention change, and generally report a greater reduction in BP. However, the results of feeding trials are less generalizable to clinical practice where provision of patient meals is infeasible. The DASH trials that have employed a behavior change strategy provide a better indication of what can be expected in clinical practice settings. In the original short-term (8-week) feeding trial, the DASH diet reduced SBP/DBP by 5.5/3.0 mmHg compared with the usual U.S. diet. In longer-term (6-month) behavior change trials, the DASH diet combined with other established nonpharmacologic recommendations for BP lowering reduced SBP and DBP by ~4 mmHg and 3 mmHg, respectively, compared to an advice-only intervention, and by 0.6 mmHg and 0.9 mmHg, respectively, compared to other established recommendations on their own. With good adherence, one could reasonably expect use of the DASH diet on its own to result in an average SBP reduction of ~5 mmHg in patients with and 2–3 mmHg in patients without hypertension. Community-based trials have dem onstrated that the DASH diet components can be purchased at super market locations without the need for patients to pay for higher priced specialty food products. The DASH diet can be combined with other

nonpharmacologic interventions such as weight loss, sodium reduc tion, or increased physical activity. Likewise, the DASH diet eating plan can be customized to meet an individual’s other dietary requirements, meal preferences, and lifestyle.

CHAPTER 288 SBP ≥140 or DBP ≥90 mmHg (Stage 2 Hypertension) Assess patient’s overall risk of ASCVD Hypertension At high risk for ASCVD Prior CVD, or No CVD but high risk of CVD

- using risk calculator
- using phenotype
  - stage 1 HTN and age ≥65, or DM, or CKD Antihypertensive drug therapy in addition to nonpharmacologic therapy Weight Loss Weight loss not only lowers BP but can also improve lipid levels and is effective for prevention and management of diabetes mellitus. It can be achieved through a combination of calorie reduc tion and increased physical activity. The most sustainable approach to weight loss is targeting gradual and progressive loss in weight. As with all behavior change strategies, weight loss can be difficult to achieve and even more difficult to maintain over long periods of follow-up. However, it can be successful, especially in motivated patients who receive high-quality counseling and clinician reinforcement. In addi tion to clinic-based interventions, many commercial and noncommer cial providers offer weight loss programs. The commercial programs usually provide some or all of the recommended meals. The optimal goal is achievement of an ideal body weight, but any weight reduction is beneficial. Application of high-quality weight loss counseling usu ally results in 6- to12-month weight loss of ~10 lb (4.5 kg). Typically, a 1-mmHg reduction in SBP can be expected for about every kilogram of weight loss. This translates to a 6- to 12-month average reduction in SBP of ~5 mmHg. The average reduction varies depending on the success of the intervention and the starting level of BP, with SBP reduc tions in those with and without hypertension tending to be about 5 and 2–3 mmHg, respectively. Several medications can be used to assist in weight loss, but some of the most popular agents, like sodium-glucose cotransporter 2 (SGLT2) inhibitors, are off-label options and are best reserved for U.S. Food and Drug Administration (FDA)-approved indications. Injectable glucagon-like peptide 1 (GLP-1) receptor ago nists are equivalent agents that have been approved for weight loss by the FDA and have been shown to reduce weight in clinical trials. Cer tain patients with hypertension and a body mass index ≥35 kg/m2 may be candidates for bariatric surgery. Selection of candidates for bariatric surgery is best conducted by multidisciplinary teams with experience in managing morbid obesity. Dietary Sodium Reduction Many RCTs have demonstrated reductions in BP following decreases in dietary sodium intake. In a large dose-response meta-analysis of RCTs, there was a striking almost linear relationship between reduction in dietary sodium intake and

the corresponding decreases in BP. This finding was quite robust, being noted for every subgroup studied. An SBP/DBP difference of ~15/10 mmHg was noted between those with the highest (~7000 mg/d) and lowest (<1000 mg/d) intakes of sodium. An average reduction of ~5.5 mmHg was noted for every 2300-mg (100-mmol) decrement in dietary sodium intake. As expected, the effect was greater in adults with compared to those without hypertension and in SBP compared with DBP. The results were consistent with a “lower is better than higher” conclusion for intake of

dietary sodium. In healthy U.S. adults, consumption of a diet with 1500 mg sodium provides adequate opportunity to meet the other recommended dietary requirements. Recommendations for daily sodium intake in adults vary considerably. The U.S. federal Dietary Guidelines for Americans recommends a daily sodium intake <2300 mg, whereas the World Health Organization recommends <2000 mg and others recommend much lower intakes. More than 95% of U.S. adults exceed the 2000 mg/d threshold, and almost 100% exceed the 1500 mg/d threshold. However, any reduction in dietary sodium intake is likely to be beneficial.

PART 6 Disorders of the Cardiovascular System The traditional approach to reducing dietary sodium intake in clini cal settings is by means of behavior change interventions. In addition to helping patients estimate and track their sodium intake, trying to avoid high-sodium foods and maximizing home preparations using fresh, natural foods are desirable. In countries like the United States, where most of the population consume commercial food products, >80% of an individual's sodium intake is generally due to sodium added during food processing or commercial preparation of foods and only ~10% is due to naturally occurring sources of sodium. Careful scrutiny of food labels for packaged foods while shopping, reducing meal portion size, choosing condiments and seasonings with low sodium content, salt substitution using herbs and spices, and use of salt substitutes that replace ~25% of the sodium content with potassium are other well-proven strategies to reduce dietary sodium intake. Salt substitutes provide a relatively easy and well-accepted way to achieve a mod est reduction in sodium intake and an increase in potassium intake, especially in those who primarily eat foods prepared in the home and/ or add a lot of salt at the table. A large cluster-designed clinical trial conducted in Chinese adults with stroke or at high risk for stroke dem onstrated an impressive and statistically significant 14% reduction in stroke (the primary outcome), other major CVD events, and all-cause mortality in adults randomized to use a salt with 25% substitution of potassium for sodium compared to those who used regular salt. There was no evidence of a difference in hyperkalemic events in the two treat ment groups. Public health messaging based on simple educational and action recommendations is also useful. Policy aimed at reducing the amount of sodium added to foods has great potential but has been difficult to implement in the United States. Long-term follow-up for 10–15 years in participants who had been randomized to a behavioral change sodium reduction intervention or usual care has also suggested a significant reduction of 30% in new-onset CVD events. Potassium Supplementation A higher intake of potassium is associated with a lower BP and a reduced risk of CVD, especially stroke. U.S. Dietary Reference Intake committees have not made a dietary allowance intake recommendation due to insufficient evidence but have identified 2600 and 3400 mg/d in women and men, respec tively, as adequate intake levels. Individual RCTs and meta-analyses provide strong evidence that potassium supplementation reduces BP. This has been achieved with pill therapy and dietary supplementation, with the latter being the preferred approach in clinical practice because this usually results in consumption of a more heart-healthy diet and a lower intake of dietary sodium. In most RCTs, routine potassium intake has been supplemented by about 2300 mg (60 mmol) per day, and the average reduction in SBP has been ~5 mmHg in trials with a successful intervention (net change in urinary potassium ≥20 mmol [870 mg] per day). As expected, the SBP reduction is greater in adults with (~5 mmHg) than without hypertension (~2 mmHg) trials. The SBP lowering is almost three times greater in black compared with white adults. Finally, there is a strong linear association between BP reduction with potassium supplementation and consumption of

dietary sodium, possibly reflecting the well-known natriuretic effects of potassium. A dose-response meta-analysis has suggested a U-shaped BP response to potassium intake, with an optimal supplemental intake of ~1200 mg/d. However, the unexpected BP response findings at the upper and lower end of the U-shaped curve were based on indirect estimates and a relatively small number of trials. Many foods contain potassium, but fruits, vegetables, legumes, and leafy greens are especially high in potassium content. By design, the DASH diet targets provision of 4700 mg of potassium per day, exceed ing the recommended intake of 3500 mg/d in U.S. adults. Potassium supplementation is contraindicated in patients with hyperkalemia or advanced kidney disease and in those taking pills that can block the urinary excretion of potassium, including potassium-sparing diuretics, inhibitors of the RAAS, and MRA agents, such as aldosterone, eplere none, and finerenone. Physical Activity Observational studies identify a strong inverse association between physical activity (leisure time or total) and BP as well as CVD. In like manner, high-quality RCTs have demonstrated that increased physical activity lowers BP in adults with and without hypertension. Most of the trials have been based on aerobic exercise interventions such as brisk walking, swimming, or dancing. Metaanalyses of aerobic exercise RCTs have been consistent in document ing substantial BP-lowering efficacy, but the quantitative estimates for average reduction in BP have varied considerably, with reports of 5–10 mmHg for SBP in studies restricted to adults with hypertension and 3–5 mmHg for studies in those without hypertension. Dynamic resistance exercises such as climbing stairs, push-ups, weightlifting, and squats have also been shown to lower BP and are often employed concurrently with aerobic exercise. Isometric resistance exercises, during which muscles or muscle groups are tightened without any visible movement of the surrounding joints, include yoga poses, wall sit, plank, and bench press exercises. Fewer high-quality RCTs have assessed the efficacy of isometric resistance exercise, but individual trials and meta-analyses indicate this approach is effective for BP lowering. In the largest meta-analysis (~400 trials) of physical activity, aerobic exercise reduced SBP by ~5 mmHg in adults with hypertension and when combined with dynamic resistance exercise by ~6.5 mmHg. In trials that allowed for a direct comparison with antihypertensive drug therapy, physical activity yielded an almost identical level of BP lowering. Most guidelines recommend moderate-intensity aerobic exercise as the principal approach to lowering BP but acknowledge that dynamic and isometric resistance exercises are a useful comple ment. Based on clinical trial evidence, an aerobic exercise duration of 40–60 min three or more times per week for a total ≥150 min per week may be optimal. Although more intensive physical activity may be ideal for overall cardiac fitness, less intensive physical activity is sufficient for BP reduction. Less frequent but more intensive physical activity (e.g., “weekend warrior” exercise) has been shown to lower BP. Alcohol Consumption Alcohol has long been known to be a pres sor. Observational dose-response meta-analyses demonstrate a roughly linear association between alcohol consumption and both BP and hypertension, with no threshold for the association. For each 14-mg increased intake of alcohol (amount in a U.S. standard alcoholic drink), SBP is ~1.5 mmHg higher. RCTs have studied the efficacy of reducing alcohol intake on BP by substitution of lower-alcohol or no-alcohol drinks, use of behavior change interventions, or abstinence without access to alcohol. The overall effect of alcohol reduction on SBP in the largest meta-analysis was a reduction of ~5.5 mmHg. However, the magnitude of the effect is greatly influenced by baseline level of BP and alcohol intake and by the success of the intervention. Most current U.S. guidelines recommend an alcohol intake goal of ≤2 and ≤1 standard drinks per day for men and women, respectively. In part, this reflects the possibility that a modest intake of alcohol may favorably influence other CVD risk factors, such as high-density lipoprotein cholesterol. The WHO recommends abstinence from alcohol. Summary for

Nonpharmacologic Interventions to Lower BP In summary, a strong body of evidence supports the value of

interventions based on the six exposures highlighted in Table 288-2. In general, the interventions exhibit a linear-type dose-response for BP reduction. Consequently, more successful interventions result in greater BP reduction, and even smaller than desired changes in the exposure are likely to be beneficial. In addition, greater BP lowering can be expected in adults with compared to adults without hyperten sion, in those who start with more abnormality in the exposure, and when two or more interventions are combined. For example, a greater reduction in BP can be expected when the intervention combines the DASH diet with weight loss or sodium reduction. However, the behav ioral changes needed for combination interventions are typically more challenging and require a greater commitment by the therapist and patient. Finally, nonpharmacologic interventions often enhance the effect of antihypertensive medications. This has been especially well demonstrated for reductions in sodium intake. A practical approach is to focus initially on the behavior that is most abnormal and most amenable to change, with a longer-term goal of more comprehensive improvements. With the exception of salt substitution, change in BP has been the primary outcome in most of the nonpharmacologic treat ment trials, but some have demonstrated improvements in intermedi ate CVD outcomes, especially left ventricular mass and left ventricular hypertrophy. In addition, randomized comparisons following long periods of posttrial follow-up have suggested CVD benefits for both sodium reduction and weight loss. ■ ■PHARMACOLOGIC THERAPY TO PREVENT CARDIOVASCULAR DISEASE Efficacy of Pharmacologic Therapy in Uncomplicated Primary Hypertension In most adults, primary hypertension is uncomplicated and relatively easy to manage. The introduction of diuretics in the late 1950s and early 1960s revolutionized pharmaco therapy of high BP, and these drugs were the principal agents in the early antihypertensive drug treatment trials. The first antihypertensive drug RCT reported a substantial benefit of active therapy compared to placebo in 1966, but it was quickly superseded by two larger placebocontrolled multicenter Veterans Administration Cooperative Group RCT analyses. The first analysis was for adults with an average DBP between 115 and 129 mmHg, and this component was stopped early due to benefit and published in 1967. The second analysis, for adults with an average DBP between 90 and 114 mmHg, was published in 1970. Both analyses demonstrated that antihypertensive drug therapy resulted in a dramatic CVD benefit compared to placebo. Subsequent trials confirmed these findings and documented benefits when SBP reductions were targeted, either in combination with an elevated DBP or as an isolated elevation of SBP in older adults. In a group metaanalysis of 123 trials, active treatment resulted in a reduction of major CVD (20%), CHD (17%), stroke (27%), HF (28%), and all-cause mor tality (13%). In this and other meta-analyses, the relative reduction in risk has been almost identical for those with or without prior CVD, albeit only adults at high risk for CVD could participate in the included trials, and benefit has accrued to those with a baseline SBP from 130 to 139 mmHg and above. Choice of Antihypertensive Drug Classes Characteristics of the 11 most commonly used classes of antihypertensive medication, including examples, usual daily dosage, frequency of administration, proposed mechanism of action, approximate BP lowering compared to placebo, most common side effects, frequency of adverse events, and special aspects of the drug class are shown in Table 288-4. Initial therapy with agents from five classes of drug therapy (diuretics, beta blockers, CCB, ACEI, and ARB) has been shown to prevent CVD compared to placebo. However, in head-to-head RCTs, beta blockers have been inferior to agents from the other four antihypertensive drug classes, especially for prevention of stroke. CCBs are good for preven tion of stroke but inferior for

prevention of HF, especially compared to diuretics. Generally, meta-analyses have identified diuretics as being the “best in class” for first-step prevention of CVD. Recognizing these differences in antihypertensive drug classes, RCTs and meta-analyses also provide evidence that BP lowering, however achieved, is more

important than the drugs used to achieve it. Most clinical practice guidelines, including the U.S. ACC/AHA BP guideline, recommend an approach similar to that outlined in Fig. 288-4 in which diuretics, CCBs, and ACEIs or ARBs, alone or in combination, are used for initial drug therapy in patients without a compelling indication for use of a beta blocker.

CHAPTER 288 One or more nonpharmacologic therapies should be used to man age adults with stage 1 hypertension who are not at high risk for CVD (no CVD and a calculated 10-year risk of ASCVD <10% based on use of the ACC/AHA pooled cohort equations calculator). If BP cannot be controlled to an SBP/DBP <130/80 mmHg after 6 months of nonphar macologic therapy, it may be reasonable to add an antihypertensive medication, especially in younger adults with a high lifetime risk of ASCVD. The latter can be estimated using a calculator that is readily available on the ACC website and elsewhere. Antihypertensive drug therapy should be used in addition to nonpharmacologic therapy in adults with stage 1 hypertension who are at high risk for ASCVD and for all individuals with stage 2 hypertension. A minority of such persons with an average SBP/DBP close to 130/80 mmHg can be man aged successfully with single antihypertensive agent combined with nonpharmacologic therapy. However, most patients with hypertension require treatment with more than one antihypertensive agent. This is especially the case for adults with stage 2 hypertension with an SBP ≥140 mmHg and all non-Hispanic black adults with hypertension. Hypertension In clinical practice settings, it is common for patients with hyperten sion to have other comorbid conditions, including diabetes mellitus, CHD, and CKD, requiring use of agents from other drug classes that concurrently lower BP. Longer-acting versions of the recommended four first-step drug classes should be used to ensure the adequacy of once-daily treatment. For example, longer-acting diuretics such as chlorthalidone or indapamide are preferred over shorter acting agents such as hydrochlorothiazide because the long half-life of these agents is better suited for the provision of nighttime as well as daytime control of BP and because chlorthalidone has been used in almost all of the land mark U.S. trials of antihypertensive drug treatment. The most common side effects with thiazide and thiazide-like diuretics are biochemical changes, such as hypokalemia and slight increases in blood glucose. Potassium-sparing agents, such as amiloride or triamterene, can be combined with diuretics to counter these effects. The biochemical changes with diuretics are generally mild and do not counteract their well-proven CVD benefits. Although there are differences between individual ACEI agents, their clinical effects are more similar than dif ferent. Use of longer-acting agents such as lisinopril is preferred. The most common problematic side effect with ACEIs is a dry cough. This side effect is usually resolved quickly by switching to a corresponding dosage of an ARB. Side effects with ARBs are rare. ACEIs and ARBs should not be used in combination because this unnecessarily increases the risk of hyperkalemia, especially in vulnerable patients and provides little if any additional benefit over using either drug class on its own. Neither an ACEI nor an ARB should be used in pregnancy or planned pregnancy due to the risk of teratogenic side effects in the fetus. In contrast to the other antihypertensive drug classes, there are substantial clinical differences between dihydropyridine and nondihydropyridine CCB agents, with the former being primarily vasoactive and the latter having greater effect on the heart. Typically, dihydropyridine CCBs should be used in the treatment of hypertension. Peripheral

edema occurs in ~10% of patients taking dihydropyridine CCBs but is often mild and can be minimized by dose reduction or eliminated by switch ing to an agent from another class. Nondihydropyridine CCBs should rarely be employed to treat hypertension unless there is another compelling indication for their use. Particular caution is necessary in patients at risk for bradycardia, heart block, or HF. The earliest beta blocker drugs were relatively nonselective block ers of β-adrenergic receptors, including the heart (β1 receptors) and lungs (β2 receptors). They are rarely prescribed for hypertension due to the potential for bronchospasm. The second class of beta blocker agents, including metoprolol, contain more cardioselective and longeracting drugs. Although cardioselective, atenolol is not recommended because several meta-analyses have reported that it has been less

TABLE 288-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure DOSE RANGE, mg DOSE FREQUENCY/D METHOD OF ACTION CLASS EXAMPLES PART 6 Disorders of the Cardiovascular System First-Step Drugs Diuretics (thiazide and thiazide-like). Chlorthalidone Hydrochlorothiazide Indapamide 12.5–25 12.5–50 1.25–2.5

Block sodium reabsorption in distal convoluted tubule ACE inhibitors Enalapril Lisinopril Benazepril Ramipril Trandolapril 5–40 10–40 10–40 2.5–20 1–4 1 or 2

1 or 2

Inhibit ACE activity and Ang II production ARB Losartan Valsartan Azilsartan Candesartan Olmesartan 50–100 80–320 40–80 8–32 20–40 1 or 2

Block Ang II binding to Ang receptors CCB (DHP) Amlodipine Felodipine Nifedipine LA 2.5–10 2.5–10 30–90

Blocks calcium from entering cells, primarily inhibiting vasoconstriction CCB (non-DHP) Diltiazem ER Verapamil ER 120–360 100–300

(evening administration recommended) Blocks calcium from entering cells, reducing heart rate and vasoconstriction Other Drugs β-Blocker Metoprolol Carvedilol Nebivolol 50–200 20–80 5–40

Block β-adrenergic receptors MRA Spironolactone Eplerenone Finerenone 25–100 50–100 10–20

Block distal tubule mineralocorticoid receptor activity K+-sparing diuretics Amiloride Triamterene 5–10 50–100 1 or 2 1 or 2 Block distal tubule sodium reabsorption

SBP REDUCTION VERSUS PLACEBO, mmHg (APPROXIMATE) MOST COMMON ADVERSE EFFECTS FREQUENCY OF ADVERSE EVENTS COMMENTS

Hyponatremia Hypokalemia Hypercalcemia Hyperuricemia Hyperglycemia Dyslipidemia Similar to placebo Chlorthalidone preferred due to long half-life and use in most U.S. trials 12.0 Cough Hyperkalemia in CKD AKF in severe bilateral RAS Hypotension Angioedema Similar to placebo Do not use in combination with ARB; contraindicated in pregnancy

Hyperkalemia in CKD Reduced GFR AKF in severe bilateral RAS Hypotension Similar to placebo Do not use in combination with ACE inhibitor; contraindicated in pregnancy

Peripheral edema (dose-dependent) Gingival hyperplasia Similar to placebo Amlodipine may be preferred CCB if tolerated Not recommended in HFrEF 9.0 Bradycardia Nausea Constipation. Similar to placebo Do not use in combination with β-blockers Do not use in HFrEF or in highgrade AV or SA block

Asthma Bradycardia Fatigue Exercise intolerance Impaired concentration Similar to placebo First-step drugs when clinically indicated, e.g., in IHD and HF Contraindicated in high-grade heart block

Hyperkalemia, especially in CKD and with potassiumsparing agents Spironolactone may cause tender breasts, gynecomastia, and erectile dysfunction in men 9–20% Especially useful in resistant hypertension and low-renin states NA Hyperkalemia, especially in CKD or with other agents that favor potassium retention Similar to placebo Minimal effect on BP Used to counteract hypokalemic effect of diuretics (Continued)

TABLE 288-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure DOSE RANGE, mg DOSE FREQUENCY/D METHOD OF ACTION CLASS EXAMPLES Loop diuretics Furosemide Torsemide 20–80 5–10

Inhibits reabsorption of sodium in loop of Henle Doxazosin 1–16

Inhibit α1-adrenergic receptors α1-Receptor blockers Direct vasodilator Hydralazine Minoxidil 100–200 5–100 2 or 3 1–3 Dilate peripheral arterioles Central α2-agonist and other centrally acting drugs Clonidine (oral) Clonidine patch Guanfacine Methyldopa 0.1–0.8 0.1–0.3 0.5–2.0 250–1000

1/wk

2–3 Stimulate central nervous system α2adrenergic receptors Note: Adverse event estimates based on U.S. Food and Drug Administration labeling at http://dailymed.nlm.nih.gov/dailymed/index.cfm. Estimates of BP lowering versus placebo are “artificially” higher with older agents than with newer agents because the former were compared to placebo alone, whereas the latter were evaluated in patients who were already being treated with other antihypertensive medications. Abbreviations: ACE, angiotensin-converting enzyme; AKF, acute kidney failure; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DHP, dihydropyridine; ER, extended release; GFR, glomerular filtration; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; LA, long acting; MRA, mineralocorticoid receptor antagonist; NA, not applicable; RAS, renal artery stenosis; SA, sinoatrial. cardioprotective than other drug classes, including diuretics, when used for treatment of hypertension. The third-generation beta blocker drugs are cardioselective and have additional vasodilatory properties (nebivolol), used alone or in combination with α-receptor blockade (carvedilol). No RCT has documented improved CVD event protection with use of the newer agents. The remaining agents in Table 288-4 are covered in other sections of this chapter. It has become increasingly clear that starting with lower doses of a two-drug combination provides superior BP control and results in fewer side effects compared to use of a single drug at a high dose. Initial

therapy is especially important because surveys of clinical practice have repeatedly demonstrated that the initial drug choice is often materially unaltered due to therapeutic inertia despite unsatisfactory BP control. RCTs using stepped-care drug therapy, in which antihypertensive medications are added sequentially if BP control has not been achieved at full doses of the proceeding drugs, demonstrate that this approach can be successful if well applied. However, initial combination drug therapy has proven to be more effective for rapid achievement of target BP and medication adherence compared to the stepped-care approach.

(Continued) SBP REDUCTION VERSUS PLACEBO, mmHg (APPROXIMATE) MOST COMMON ADVERSE EFFECTS FREQUENCY OF ADVERSE EVENTS COMMENTS CHAPTER 288 NA Hypokalemia Volume depletion Hyperuricemia Infrequent Preferred in CKD with GFR <30, in symptomatic HF, and when using potent direct vasodilator minoxidil Hypertension

Orthostatic hypotension, especially in older adults 9% Less cardioprotective than diuretics Mostly used in men with prostrate hypertrophy NA Reflex tachycardia Fluid retention Hydralazineinduced lupus syndrome (rare) Minoxidil-induced hirsutism in women Up to 80% Potent antihypertensive agents Usually reserved for fourth- or fifthstep treatment in resistant hypertension Usually combined with diuretic (loop agents for minoxidil) and β-blocker to minimize side effects NA Sedation Dry mouth Bradycardia Fatigue Constipation Orthostatic hypotension. 6–20% Infrequently used due to side effects and potential for hypertensive crisis following abrupt withdrawal Methyldopa has a good safety record in pregnancy Antihypertensive drug combinations should be based on use of drugs with complementary physiologic actions. For example, a diuretic or CCB combined with an ACEI or ARB is suitable for dual therapy and a diuretic combined with a CCB and an ACEI or ARB for tripletherapy combinations. Use of single-pill combinations results in better adherence compared to treatment with multiple drugs. In RCTs, the average number of drugs to achieve an SBP/DBP <140/90 mmHg has been two and to achieve an SBP/DBP <130/80 mmHg has been three. Antihypertensive Treatment Blood Pressure Target Many clinical trials have reported better prevention of CVD in groups ran domized to lower compared with higher achieved treatment BPs. Metaanalyses of RCTs to compare different achieved BPs have typically pooled the experience in trials that compared active versus placebo treatments, more versus less intensive treatments, and groups random ized to different BP targets. Most of these meta-analyses have reported greater benefit for a lower versus higher achieved BP, with the ben efit being greatest for those who start at a higher BP and achieve a greater reduction in BP that their counterparts who achieve the

Nonpharmacologic therapy (only)

- Heart healthy diet, especially DASH diet
- Weight loss
- Dietary sodium reduction
- Potassium supplementation
- Physical activity
- Abstinence/reduced alcohol consumption PART 6 Disorders of the Cardiovascular System Add antihypertensive drug therapy Initial monotherapy in selected nonblack adults with stage 1 hypertension whose average SBP/DBP is close to 130/80 mmHg
- diuretic, CCB, ACEI, or ARB FIGURE 288-4 Overview of specific antihypertensive treatments in adults with uncomplicated hypertension. ACEI, angiotensin converting

enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; MRA, mineralocorticoid receptor antagonists; SBP, systolic BP. same BP but start from a lower level of BP. As one would expect from the observational association between BP and CVD, the incremental benefit for CVD protection diminishes as the category of achieved BP gets progressively lower. Almost all of the meta-analyses, including one conducted for the ACC/AHA BP clinical practice guideline com mittee, have reported that an achieved SBP of <130 mmHg is superior to higher categories of achieved SBP. The major English-language clinical practice guidelines recommend SBP treatment targets that vary from 120 to 135 mmHg in adults with hypertension and a high risk of ASCVD. Surveys indicate that almost all patients with hypertension who are seen in clinical practice are at high risk for ASCVD. At the cur rent time, an SBP/DBP treatment goal of 130/80 mmHg in adults with hypertension, as recommended in the ACC/AHA BP guideline, seems reasonable. The only exception is in noninstitutionalized communitydwelling older adults, arbitrarily defined as ≥65 years, where the goal should be to achieve an SBP <130 mmHg. For older adults with hypertension and a high burden of comorbidity who have a limited life expectancy, clinical judgment and patient preference should form the basis for decisions regarding the potential value and intensity of BP treatment. An SBP/DBP treatment goal of <130/80 mmHg should not preclude the possibility of achieving a greater reduction in BP in those who tolerate their BP-lowering treatment without evidence of adverse effects. In all four of the RCTs that have compared randomization to an SBP goal of 120 versus 140 mmHg, fewer CVD complications have been noted in the group assigned to the lower BP, albeit this has only been statistically significant in two of the four trials. Three additional large 120 versus 140 mmHg RCTs are expected to report in the near future, which should result in more definitive guidance for a 120 versus 130 mmHg SBP target. Resistant Hypertension Failure to control SBP/DBP to <130/80 mmHg with three antihypertensive medications, prefer ably including a diuretic, or taking four or more antihypertensive medications to achieve an SBP/DBP <130/80 mmHg is designated as apparent resistant hypertension. A general approach to the investigation and management of apparent resistant hypertension is outlined in Fig. 288-5. First, pseudo-resistance due to inaccurate BP measurement should be excluded. Next, accurately measured out-of-office BP readings should be obtained to exclude white coat hypertension. After this important issue is addressed, lifestyle, OSA, use of medications that

Initial combination drug therapy in most patients, especially in black adults and those with an average SBP >20 mmHg above treatment goal

- diuretic or CCB combined with ACEI or ARB
- single-pill combinations preferred, if feasible Triple-drug therapy if SBP/DBP remains >130/80 mmHg
- diuretic, CCB, and ACEI or ARB If SBP/DBP remains >130/80 mmHg (resistant hypertension)
- consider adding MRA, and vasodilators, if needed
- If still uncontrolled, add other agents, or refer to specialist raise BP, and other secondary causes of hypertension should be excluded. Management of resistant hypertension starts with confirma tion of adherence to the prescribed treatment regimen because lack of

adherence to lifestyle change advice and medication nonadherence are common explanations for apparent resistant hypertension. It is also important to ensure that the medication regimen is based on use of long-acting, once-daily agents. This is especially true for diuret ics, where shorter acting agents such as hydrochlorothiazide should be replaced by chlorthalidone or indapamide. If the antihypertensive medications have been prescribed as separate pills, conversion to a single pill combination is highly desirable. After this issue is addressed, an MRA such as spironolactone should be added to the regimen (Table 288-4). Most patients tolerate spironolactone, but in a minority, laboratory abnormalities such as hyperkalemia or side effects such as dizziness, leg cramps, and gynecomastia can be troublesome, especially in men. Many of the spironolactone side effects can be avoided by use of newer but more expensive MRA agents such as eplerenone and, especially, the nonsteroidal finerenone. In 2023, the U.S. FDA approved the use of ultrasound and radiofrequency renal denervation therapy as adjunctive treatments in patients with resistant hypertension. Consider ation of renal nerve denervation (RDN) should be restricted to patients with true resistant hypertension and an office SBP ≥160 mmHg. Treatment of Hypertension in Special Groups Certain patient groups have characteristics that warrant special attention. The follow ing are some of the more important groups. PATIENTS WITH CVD The combination of hypertension and CVD is very common. Choice of antihypertensive agents is commonly influ enced by the specific type of CVD, but use of ACEI, ARB, or beta blockers is common, often accompanied by diuretics, CCB, and MRA. Additional treatment with SGLT2 inhibitors may be indicated, espe cially in those with HF and diabetes mellitus. Nondihydropyridines should be used with caution in patients with bradycardia or the poten tial for heart block. In general, the standard treatment goal of SBP/DBP <130/80 mmHg is indicated if well tolerated. KIDNEY DISEASE Hypertension is very common in patients with CKD, becoming more prevalent with increasing severity of CKD, such that 80–85% of those with advanced kidney disease have concurrent hypertension. High BP is a risk factor for CKD and ESKD, but the inter action between BP and kidney disease is complex, making it difficult

Confirm resistant hypertension diagnosis

- SBP/DBP ≥130/80 mmHg on triple antihypertensive drug therapy, preferably including a diuretic
- SBP/DBP <130/80 mmHg but taking ≥4 antihypertensive medications
- BP levels confirmed with accurate measurements
- Treatment nonadherence apparently excluded
- Out-of-office BPs exclude white coat hypertension Lifestyle, OSA, medication use, and other secondary causes of hypertension
- Unhealthy lifestyle: poor-quality diet, overweight/obese, consuming excessive dietary sodium or insufficient potassium, physically inactive, excessive alcohol consumption
- Obstructive sleep apnea
- Medication and other substances that raise BP
- Anatomic causes: renal parenchymal disease, primary aldosteronism, renovascular disease, hypertensive disorders of pregnancy etc.
- Reaffirm importance adherence to lifestyle and antihypertensive medication regimen
- Ensure use of long-acting diuretic at full dosage

- Add an MRA as fourth medication
- Add vasodilator (hydralazine or more potent minoxidil)
- Consider referral to appropriate specialist if:
- Anatomical secondary cause detected
- BP still uncontrolled after 6 months of treatment FIGURE 288-5 Confirmation and management of resistant hypertension. BP, blood pressure; DBP, diastolic blood pressure; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; SBP, systolic blood pressure. to determine cause and effect. Patients with kidney disease have a high prevalence of both traditional and novel risk factors for CVD, includ ing markers of inflammation and endothelial dysfunction. As a result, the burden of CVD complications is high in adults with kidney disease, and patients with ESKD are more likely to die from CVD than from other complications of kidney failure. Managing hypertension in adults with advanced kidney disease can be difficult because they frequently have a combination of increased vascular resistance and intravascular volume overload and can exhibit vascular instability with wide swings in BP that complicates management. Normally, preglomerular vaso constriction decreases the pressure to which the glomerulus is exposed and optimizes filtration without damaging the glomerulus. The effer ent glomerular arteriole can play a supplementary role, as needed, to regulate intraglomerular pressure. When kidney disease is present, the ability to regulate intraglomerular pressure is diminished, with the result that it rises and results in physical damage, a pathophysiologic process that often manifests in proteinuria and diminished glomerular filtration as the number of functioning nephrons declines. Generally, patients with kidney disease and hypertension require several antihypertensive agents in addition to nonpharmacologic counseling, especially focused on sodium reduction. Antihypertensive drugs that block the RAAS such as ACEIs and ARBs play a central role because they can preserve glomerular function by inducing effer ent arteriolar dilatation and reducing intraglomerular pressure. They are particularly important in patients with proteinuria and advanced kidney disease. Diuretics also play an important role because they can concurrently reduce peripheral resistance and intravascular volume. Traditionally, loop diuretics have been recommended in place of thia zide or thiazide-like diuretics in patients with an eGFR of ~30 mL/min per 1.73 m2 or lower, but a recent high-quality RCT in patients with stage 4 kidney disease (average eGFR <23 mL/min per 1.73 m2) dem onstrated substantially lower (10.5 mmHg) reduction in ambulatory BP and a halving of urinary albumin/creatinine ratio in those randomized to chlorthalidone (12.5–50 mg) compared to placebo. Although CCBs tend to dilate the preglomerular afferent artery, they have a good safety record in kidney disease patients when used in combination with an ACEI or ARB. Single-pill antihypertensive combinations are especially

CHAPTER 288 Exclude Hypertension Management useful in patients with kidney disease because they are usually taking a large number of medications. Electrolyte levels should be monitored carefully, especially serum potassium levels, in kidney disease patients who are treated with potassium-sparing agents, including ACEI, ARB, and MRA drugs. Dual therapy with an ACEI, ARB, or ACEI-ARB com bination is dangerous because of the risk of hyperkalemia and decline in kidney function. PATIENTS WITH DIABETES MELLITUS The combination of hyperten sion and diabetes is common, resulting in a substantial risk for CVD and kidney disease. In patients with longstanding severe diabetes mel litus, autonomic neuropathy or volume depletion can cause orthostatic

hypotension (10 mmHg difference in SBP between sitting and upright pressures), making management of hypertension difficult and requir ing careful monitoring. Symptomatic hypotension (syncope) is a more important finding and may require a stepdown in antihypertensive therapy. Numerous RCTs in adults with diabetes have demonstrated that antihypertensive drug therapy reduces the risk of ASCVD, HF, and microvascular complications. The recommended antihypertensive treatment target is an SBP/DBP <130/90 mmHg. Almost all patients with hypertension and diabetes mellitus require antihypertensive com bination therapy, with many requiring three or four agents to achieve satisfactory BP control. Inclusion of an ACEI or ARB in the combina tion is recommended, especially in those with heavy proteinuria or kidney insufficiency. In addition, most patients require a diuretic. CCBs are commonly part of the antihypertensive drug regimen as well. In patients with diabetes mellitus and resistant hypertension, the addi tion of an MRA has been effective; however, serum potassium should be monitored carefully. Many drugs used to treat diabetes mellitus affect BP. Perhaps the best documented are SGLT2 inhibitors, which in meta-analyses result in an SBP/DBP reduction of ~5/2 mmHg, a mod est reduction that does not meet the FDA requirement for classification as an antihypertensive agent. Given that patients with diabetes mellitus are often taking many medications, use of single-pill dual- or triplecombination therapy is especially useful. OLDER ADULTS Vascular stiffening increases with aging, and as a result, isolated elevation of SBP and a wide pulse pressure are common

in older adults. Comorbidity is common, resulting in the potential for a compelling nonhypertensive indications for use of BP-lowering agents. Drug-drug interactions and delayed drug excretion due to kidney or liver disease are also possible. Despite these challenges, most older adults with hypertension can be treated in a manner similar to younger patients. Indeed, the RCT evidence for antihypertensive drug therapy generally comes from studies in which the average age was close to 70 years at baseline. Older adults tend to be at high risk for CVD and all-cause mortality and have a disproportionately large treatmentrelated reduction in the absolute CVD and all-cause mortality ben efit. A natural concern in treating hypertension in older adults is the potential for excessive BP reduction resulting in syncope and resultant falls, or organ hypoperfusion with resultant infarction, especially in the distribution of the coronary arteries. Thus far, RCTs of antihyper tensive drug treatment in older adults have been reassuring, resulting in substantial prevention of CVD and all-cause mortality with limited evidence of adverse events. An increased incidence of hypotension has been noted in some but not all trials of antihypertensive treatment in older adults. However, there has been no evidence of a resultant increase in syncope, falls, or infarctions in the RCTs. Nonrandomized analyses of data sets have identified a J-shaped association between BP and CVD risk. However, J-curves are common in observational epidemiology, and randomized comparisons, which are more helpful in guiding treatment decisions, have revealed prevention of CVD and all-cause mortality in those randomized to more versus less intensive antihypertensive therapy at any point in the J-curve. A reasonable approach is to initiate or enhance existing treatment using lower doses of medications than in younger patients. Because congestive heart failure becomes increasingly common at older age, use of a diuretic rather than a CCB for dual-therapy combinations with an ACEI or ARB is sensible. Many older patients require triple therapy or have comorbidities that necessitate treatment with a CCB. As is the case generally, BP lowering is more important than the treatment combina tion used to achieve the desired SBP goal of <130 mmHg. Recent trials have provided compelling evidence that more intensive antihyperten sive treatment in older adults reduces the risk of cognitive impairment compared to less intensive treatment, and increasing evidence suggests that it reduces the risk of dementia.

PART 6 Disorders of the Cardiovascular System RACE/ETHNICITY Non-Hispanic blacks have disproportionately high BP levels and higher prevalence of hypertension compared to whites and other major race/ethnicity groups in the United States. In addi tion, hypertension tends to occur earlier in life and is associated with a higher risk of CVD and kidney disease in blacks compared to whites and the other major race/ethnicity groups. Non-Hispanic blacks have the highest awareness of hypertension of any race/ethnicity group

in the United States and have an antihypertensive drug treatment rate that is at least as high as that of whites. However, their rate of control to <140/90 mmHg in the 2017–2020 NHANES survey was 15% lower than in whites (37 vs 52%) and 6% lower for the 130/80 mmHg cut point (20 vs 26%). Genetic differences seem to explain a small fraction of the high prevalence of hypertension in black Americans, but most of the disparity is likely due to differences in the social determinants of health, including access to and quality of education and health care, neighborhood of residence and the related built environment factors, economic instability, and the social and community context. The BP, CVD, and kidney disease health discrepancies between black and nonblack U.S. adults are not only sizable but have also been persistent, with little improvement in recent decades. RCT experience dem onstrates that the gap can be eliminated with high-quality care, but following termination of RCT care, there has been a relatively rapid reversion to previous patterns of inadequate BP control. Resolution of the situation is unlikely without structural change in the approach to provision of care and a multilevel effort that involves patient engage ment, a team-based approach to care that frees up clinicians to address social determinants of health, health system policies that enhance the provision of high-quality care, and payors with a focus on quality and use of contemporary BP goals for BP control. Diuretics and CCBs are especially effective for lowering BP in U.S. blacks, but many patients

require triple antihypertensive therapy, and use of BP-lowering agents for management of comorbid conditions is common. SEX Although there are well-described differences in the underlying pathophysiology of hypertension in women and men, RCT experience indicates a similar benefit in prevention of CVD in both sexes in the landmark antihypertensive drug treatment trials. In the United States, women are more likely to be aware of hypertension, to be treated with antihypertensive medication, and to achieve the desired level of BP control compared with men, especially at younger ages. ACEIs and ARBs should not be used in pregnancy or women of child-bearing age who are contemplating pregnancy. Antihypertensive agents with a good safety record in pregnancy are highlighted in the section on hypertension in pregnancy. Observational studies and RCTs, includ ing meta-analyses, have reported a reduced risk of fractures in women being treated with thiazide diuretics. This is postulated to result from decreased urinary calcium excretion and increased osteoblast cell for mation. In contrast to thiazide diuretics, loop diuretics increase urinary calcium excretion. However, analyses of large observational studies have failed to associate loop diuretic use in postmenopausal women with fractures or a decrease in bone marrow density. Women report more cough with ACEIs and more pedal edema with CCB treatment compared with men. Hypertensive Urgencies and Emergencies Adults present ing with a very high level of BP, usually designated as an SBP/DBP ≥180/100 mmHg, should be classified as having a hypertensive urgency if they are asymptomatic or a hypertensive emergency if there is evidence of active ongoing hypertensive end-organ damage such as hypertensive encephalopathy, often manifesting with headaches, vision defects, nausea, vomiting, seizures, acute left ventricular failure, or acute kidney failure. Hypertensive urgency is far more common than hyper tensive

emergency and should be treated with institution, reinstitution, or intensification of oral antihypertensive agents in an outpatient set ting. In contrast, a hypertensive emergency requires immediate, care fully supervised management with intravenous antihypertensive agents in an emergency room or inpatient setting. A hypertensive emergency associated with acute aortic dissection, eclampsia or severe preeclamp sia, or a pheochromocytoma in crisis signals the need for particularly rapid care. Several drug classes can be used intravenously to achieve a rapid reduction in BP. Intravenous sodium nitroprusside is a potent vasodilator with a long history of success in managing hypertensive emergencies but must be monitored carefully to avoid overshooting the goal BP and causing hypotension. The dihydropyridine CCB nicardip ine, given intravenously, is perhaps the most commonly utilized agent for acute BP reduction in patients with a hypertensive emergency in the contemporary practice of medicine. No dose adjustment is required for its use in older adults, but it is contraindicated in patients with severe aortic stenosis. Intravenous administration of the beta blocker labet alol is also effective but is contraindicated in patients with obstructive airways diseases, chronic obstructive pulmonary disease, bradycardia, or second- or third-degree heart block. Whichever drug is employed, a reduction rather than immediate normalization of BP is sufficient, with subsequent management of the patient's hypertension with oral agents. Secondary causes of hypertension, especially renovascular disease, are relatively common in patients with a hypertensive emergency and should be considered after the immediate reduction in BP. PREVALENCE, AWARENESS, TREATMENT, AND CONTROL OF HYPERTENSION NHANES provides a way to monitor prevalence, awareness, treat ment, and control of hypertension in the U.S. general population. The NHANES definition of hypertension is based on BPs measured at a single visit, which results in an overestimation of hypertension, and the HHANES definition of treatment and control do not take into account nondrug therapy of hypertension. However, the methods used in NHANES have been consistent and careful over time, providing very helpful estimates for the temporal trends in hypertension prevalence and BP control. NHANES hypertension prevalence estimates have been fairly stable at ~46 and 32% for definitions based on use of the

SBP/DBP cut points of 130/80 and 140/90 mmHg, respectively, with higher prevalence rates in older versus younger adults, nonHispanic blacks versus all other major race/ ethnicity groups, and men compared with women. Treatment (with antihypertensive agents) and hypertension control rates increased progressively until about 2009– 2012, with close to 53% of U.S. adults being controlled to an SBP/DBP <140/90 mmHg (the recommended goal at the time) and ~26% for an SBP/DBP <130/90 mmHg. After that, there was a progressive decline in control rates, with ~48 and 24% having an SBP/DBP <140/90 and <130/80 mmHg, respectively, by 2017–2020. The percentage controlled was higher when the analysis was confined to adults being treated for hypertension, but the temporal trends pat tern was similar. The decrement in hyper tension control was especially prominent in adults ≥75 years old. There has been a persistent gap in hypertension control rates between non-Hispanic black adults and all other race/ethnicity groups in the United States, with the percentage of non-Hispanic blacks and whites controlled to an SBP/ DBP <140/90 mmHg in 2017–2020 being ~37 and 52%, respectively (20 and 26% for an SBP/DBP <130/80 mmHg). Worldwide, the situation is worse, with a recent global estimate reporting control to an SBP/DBP <140/90 mmHg in <14% of adults and in <8% of adults in low- and middle-income countries, where most of the world's population resides. Community-based patient-centered team care Commitment by provider, system of care, or country to specific goals Health promotion for BP-lowering and antihypertensive medication augementation Manage uncomplicated hypertension

with patient-centered, team-based care Ensure access to effective and affordable meds, preferably at the point of care Use simple evidence-based protocols and algorithms for team management Engage patients in their own care with HBPM and other options Track progress and employ case management for immediate corrective actions FIGURE 288-6 Best practices for control of hypertension. BP, blood pressure; HBPM, home blood pressure monitoring. ■ ■IMPROVING THE CONTROL OF HYPERTENSION Clearly, the current hypertension control rates are unacceptable, and the traditional model of one-on-one physician-patient care for hyper tension is not yielding a satisfactory outcome. Primary care physicians, who care for most patients with hypertension, are overburdened with responsibilities and have very limited time for direct provision of care in those with “routine” uncomplicated hypertension. A number of approaches have been shown to improve hypertension control rates in RCTs and clinical practice settings. Among these, team-based care has resulted in the biggest improvement in RCTs and meta-analyses. In the typical model of team-based care for hypertension management, a physician coordinates care provided by a team that may include nurses, pharmacists, community health care workers, social workers, lifestyle counselors, medical technicians, or others who have been specially trained in the provision of hypertension care. The specifics of the team composition depend on what is feasible in a practice setting and can be extended to engage front-office staff, spouses/partners, and close friends. In RCTs, team-based care has resulted in an average SBP reduction of ~7 mmHg, but in a recent high-quality, well-executed RCT, the SBP reduction exceeded 23 mmHg. It has been especially effective when trained nonphysician professionals have had the author ity, usually with physician oversight, to prescribe antihypertensive medications in patients with uncomplicated hypertension. This frees up physician time to address patients with more complex care require ments. Most team-based care interventions have been multifaceted, incorporating health counseling, home BP monitoring (HBPM) and electronic support systems, and use of simple algorithms for health counseling and management of antihypertensive drug therapy. HBPM provides an excellent way to engage patients in their own care and to complement office BP management (OBPM) for monitoring long-term control of hypertension. Use of HBPM mandates advising patients on the purchase of clinically valid BP measurement devices and training in accurate measurement of BP (see BP measurement section). In U.S.

CHAPTER 288 Information systems to track progress and case management Reliable access to effective and affordable medication Hypertension Health Promotion Simple evidence-based tools for lifestyle counseling and drug treatment Lifestyle improvements Antihypertensive drug treatment adults, getting three morning (prior to taking BP medications) and three evening HBPM measurements for 3 days prior to a clinic visit is a reasonable strategy for assessing average home BP. Team-based care approaches have not only been successful in RCTs but also yielded excellent results in clinical practice settings, with Kaiser-Permanente, Northern California reporting an improvement in SBP/DBP control to <140/90 mmHg from 44% in 2001 to 90% in 2015 based on institution of a multifaceted systemwide program of health care quality improve ment that incorporated many of the previously mentioned approaches. Likewise, many of these approaches have been used to good effect in the U.S. Department of Veterans Affairs Health System. An overall best practices approach is outlined in Fig. 288-6. While it may not be possible for an individual practitioner to imple ment all of the suggestions in the figure, they should advocate for those that are beyond their direct control. There is great need to improve the management and control of hypertension in the United States and world wide. Hypertension is among the most important, prevalent, modifiable, and cost-effective risk factors for CVD, kidney disease, and all-cause mortality. Its detection, treatment, and control should be a high priority for individual clinicians,

systems of care, and countries worldwide. ■ ■FURTHER READING Blood Pressure Lowering Treatment Trialists, Collabora tion: Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: An individual participant-level data meta-analysis. Lancet 397:1625, 2021. Bundy JD et al: Systolic blood pressure reduction and risk of cardio vascular disease and mortality: A systematic review and network meta-analysis. JAMA Cardiol 2:775, 2017. Carey RM et al: Treatment of hypertension. A review. JAMA 328:1848, 2022. Fuchs FD, Whelton PK: High blood pressure and cardiovascular disease. Hypertension 75:285, 2020. Panagiotis G, Agarwal R: Hypertension in chronic kidney disease: Treatment standard 2023. Nephrol Dial Transplant 3:2694, 2023.

---

Revision #1
Created 2026-01-06 16:33:58 UTC by Omar Ayman
Updated 2026-01-06 16:33:58 UTC by Omar Ayman