Arterial Hypertension

2

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2.1 Introduction

High blood pressure (BP) is a very important (CV) risk factor and is often considered as the silent killer, because arterial hypertension will lead to serious cardiovascular (CV) events such as ischemic heart disease, myocardial infarction, stroke, heart failure, and peripheral arterial disease [1, 2]. Moreover uncontrolled essential hypertension will also lead to renal insufficiency, which will accelerate the process of blood pressure elevation. There is a shift regarding diagnosis and treatment of arterial hypertension. With aging systolic hypertension is becoming a more important risk factor than diastolic hypertension and is more difficult to control (Fig. 2.1).

2.2 Definition of Arterial Hypertension

For decades arterial hypertension was defined if systolic blood pressure was equal or greater than 140 mmHg and/or diastolic blood pressure was equal or greater than 90 mmHg. In November 2017 the American Heart Association/American College of Cardiology in collaboration with nine other scientific organizations announced the new guidelines for diagnosis and treatment of hypertension [3, 4]. Despite increasing BP levels being a continuous cardiovascular (CV) risk factor, the new BP guidelines considered four different categories (Table 2.1). Normal blood pressure is now defined as a SBP below 120 mmHg and a DBP below 80 mmHg. Elevated hypertension is now defined as a SBP in a BP range between 120 mmHg and 129 mmHg and DBP below 80 mmHg. Another new classification in the 2017 BP ACC/AHA guidelines is that the SBP range of 130–139 mmHg or the DBP range of 80–89 mmHg is considered as stage I hypertension and SBP equal or greater than 140 mmHg or DBP equal or greater than 90 mmHg is considered as stage 2 hypertension. The other difference with the previous guidelines is that there are no different target goals anymore for patients with diabetes mellitus (DM) and chronic kidney disease (CKD). The evidence for the new reclassification of hypertension was based on the observational findings regarding SBP and/or DBP level and CVD risk, the beneficial effects of lifestyle modification on BP lowering, and the evidence obtained from the randomized clinical trials with antihypertensive drugs and the CVD risk reduction [1, 2, 5–8]. Another rationale to lower the threshold for SBP and DBP was that with aging a high normal level at younger age was accelerating the development of hypertension and consequently increasing the CVD risk at a later age [9, 10].

2.3 Epidemiology of Hypertension

Hypertension is considered the most common reversible or treatable CV risk factor [11].

In 2010, high BP was the leading cause of death and disability-adjusted life years worldwide [12, 13]. The population attributable risk due to elevated BP is large and present in all ethnic groups and regions of the world. It is not then surprising that hypertension has been identified as a condition, which accounts for a substantial portion of total global disease burden. From a clinical perspective, there is one generally accepted cardinal principle that describes the hypertensive state and which has served to define the importance of hypertension to world health. The presence of an elevated uncontrolled BP overtime will lead to progression in the severity or stage of hypertension, the development, or wors-

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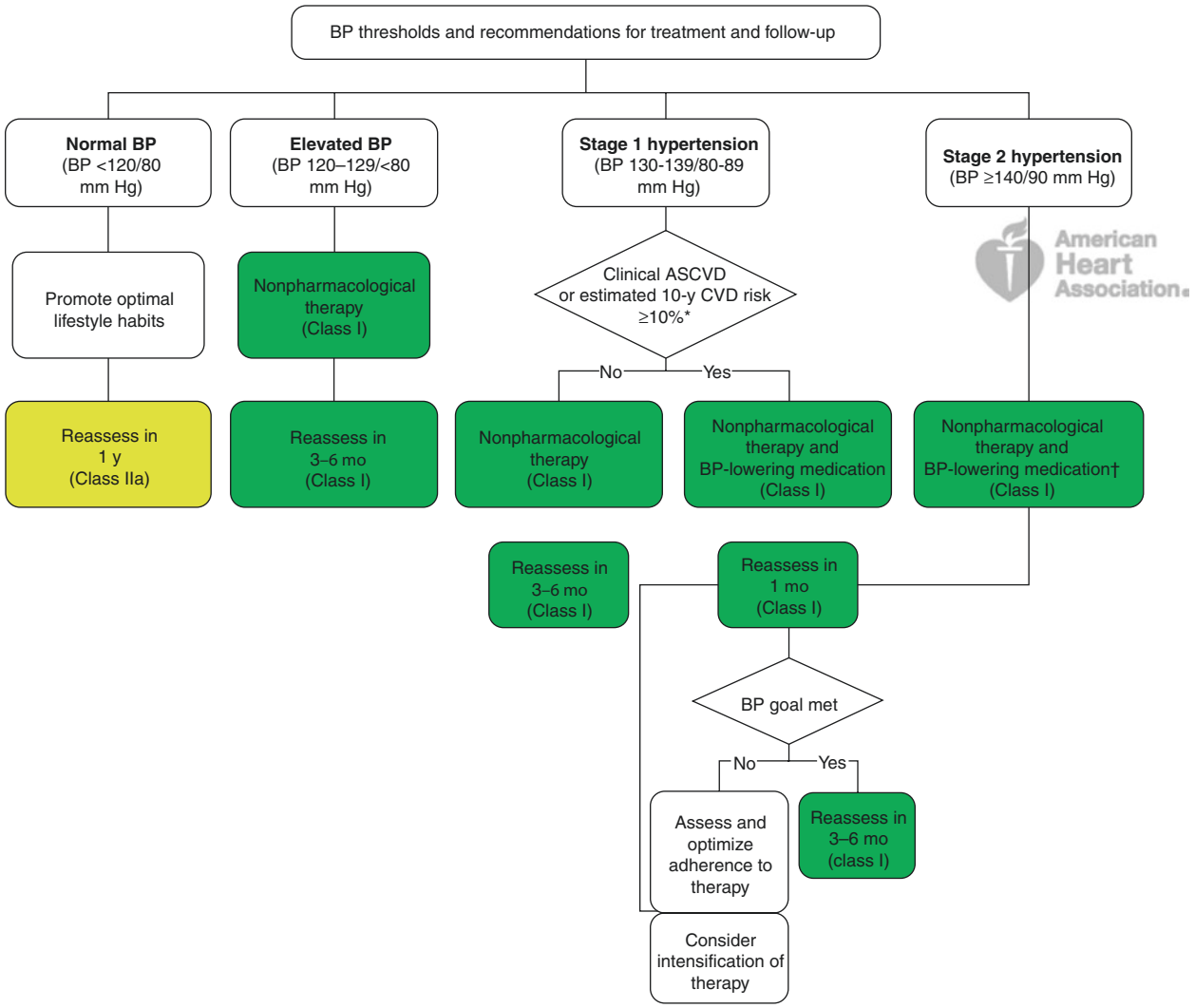

Fig. 2.1 Blood pressure (BP) thresholds and recommendations for treatment and follow-up. (Copy Fig. 4 from Whelton et al. [3])

Table 2.1 Categories of BP in adults[a]

BP category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Copy Table 6 from Whelton et al. [3]
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Sect. 2.4), *DBP* diastolic blood pressure, *SBP* systolic blood pressure
[a]Individuals with SBP and DBP in two categories should be designated to the higher BP category

ening of target organ damage and to increased CV morbidity and mortality. Given the relationship of hypertension to stroke, myocardial infarction, heart failure, and other vascular disease, the control of high BP will have a profound impact on individual well-being and national healthcare costs. Elevated BP demonstrates a consistent, strong, and graded relationship with multiple CV events including CV death, myocardial infarction, stroke, heart failure, and renal dysfunction. The risk of CV mortality has been observed to double with each 20/10 mmHg increase in BP from 115/75 mmHg in adults aged from 40 to 69 years of age. Unfortunately, a gap continues to exist between hypertension and awareness and control [14].

2.4 Mechanisms of Hypertension

The pathogenesis of essential hypertension is a heterogeneous process, and several physiological systems result in a change of the cardiovascular hemodynamics. Arterial blood

pressure is the product of cardiac output (stroke volume × heart rate) × total peripheral vascular resistance.

2.4.1 Hemodynamics

The blood pressure required to supply the different organs and tissues with blood through the circulatory bed is provided by the pumping action of the heart (cardiac output) and arterial tone (total peripheral vascular resistance). Each of these primary components is determined by the interaction of a complex series of factors. Arterial hypertension has been attributed to abnormalities in nearly every one of these factors [15, 16]. During the last decade, there has been more attention to pulse pressure, which is the difference between SBP and DBP and is a simple parameter to have some information about arterial stiffness and also an independent predictor for cardiovascular disease events [17]. There is growing information that the arterial blood pressure waveform provides more information for CV risk than the SBP and DBP value, because two BP values are only the two extreme points of the whole BP waveform [18–20].

An increase in arterial tone has traditionally been viewed as the hallmark for an elevated BP. Although some have suggested that an increase in cardiac output with a normal vascular resistance is the initial hemodynamic abnormality in patients with hypertension, the chronic hypertensive state usually is associated with an increase in total systemic vascular resistance [21]. This increase in resistance is generally attributed to an increase in vascular tone. Multiple mechanisms possibly contribute to this increase in systemic vascular resistance: activation of the sympathetic nervous system [22], the renin–angiotensin–aldosterone system (RAAS) [23], endothelial dysfunction [24], and inflammation [25].

2.4.2 Renal

The relationship between the development or pathogenesis of hypertension and the kidney is complex [26]. The kidney through a variety of distinct renal mechanisms can cause or contribute to the development or to the progression of hypertension [27]. On the other hand, hypertension per se can contribute to progressive renal structural and vascular damage, which in turn may contribute to a worsening or perpetuation of the hypertensive state. Renal functional and structural changes can promote sodium retention. Excessive sodium reabsorption can lead to plasma volume expansion, an increase in cardiac output, and ultimately an increase in total peripheral resistance and BP [28]. These mechanisms most certainly contribute to the BP elevation, which accompanies CKD and some cases of primary hypertension. Several other renal factors have received attention as potential contributors to this vicious cycle that is characterized by development of hypertension and progressive renal damage. Inappropriate or excessive activation of the RAAS in relationship to the sodium/volume balance may contribute to BP elevation, especially in the setting of renal parenchymal disease.

2.4.3 Neurohumoral Factors

Many factors are now implicated in the development of hypertensive vascular disease, and the RAAS appears to be one of the most significant. Angiotensin II, the principal effector peptide of the RAAS, has far-reaching effects on vascular structure, growth, and fibrosis and is a key regulator of vascular remodeling and inflammation. The RAAS is an important contributor to the regulation of BP, water and salt balance, and tissue growth. It functions both as a circulating endocrine system and as a tissue paracrine/autocrine system, most notably in the heart, brain, kidney, and vasculature. Aldosterone is the major mineralocorticoid hormone secreted by the adrenal cortex and plays an important role in resistant hypertension [29]. Identification of mineralocorticoid receptors in the heart, vasculature, and brain has raised speculation that aldosterone may directly mediate its detrimental effects in these target organs, independent of angiotensin II and the regulatory role of aldosterone in kidney function and BP [30].

2.4.4 Baroreflexes

The arterial baroreflex is known to represent a mechanism of fundamental importance for short-term BP homeostasis in daily life. Reduced baroreflex sensitivity appears to characterize not only patients with established hypertension but also normotensive offspring of hypertensive parents [31].

2.4.5 Aging

Available evidence suggests that the incidence of systolic hypertension is increasing in individuals over 50 years of age. There are multiple mechanisms involved [32]. These include an altered vascular resistance, the classical hallmark of high BP, as well as changes in arterial stiffness and wave reflection, which occur in the conduit arteries, mainly the aorta and its principal branches.

2.5 Etiology of Hypertension

The specific set of events that lead to progressive elevation of BP and the development of hypertension remains unknown. Depending on the clinical setting, 90% of hypertensives had no known cause for their hypertension. For that reason, most hypertension states were originally classified as essential hypertension. Primary hypertension is another terminology, which is used to compare and contrast with the secondary hypertension. In case of secondary hypertension, a cause is found, and the therapeutic strategy will be guided by the cause.

2.5.1 Primary or Essential Hypertension

Although the pathogenesis of primary hypertension is uncertain, as previously noted, specific mechanisms appear to be involved in the development of primary hypertension: altered regulation of sympathetic nervous system, cell membrane defects, renin secretion, salt sensitivity, as well as other vascular and hormonal factors. In addition to these multiple physiologic abnormalities, diet, environment, other lifestyle factors, and most certainly genetics frequently play a role in the development of hypertension.

Patients with primary hypertension are generally asymptomatic. Although some patients report symptoms related to hypertension such as headache, dizziness, fatigue, palpitations, and chest discomfort, these symptoms and their level of intensity generally do not correlate well with BP level. Thus, primary hypertension has no consistent symptoms or signs, except for the elevated BP itself. A specific type of headache has, however, been reported to occur with elevated BP. Hypertensive headache is a clinical entity, which has been described as a diffuse morning headache, and is generally associated with more severe stages of hypertension; in some circumstances these headaches may actually be associated with sleep apnea complicating arterial hypertension, rather than the BP itself.

2.5.2 Genetics

Hypertension is a complex polygenic disorder in which many genes or gene combinations influence BP. There is tremendous research going on in the field of genetics, epigenetics, transcriptomics, and proteomics which try to link the genotypes with the underlying mechanisms [33]. There are some rare monogenic forms of hypertension such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, Gordon's syndrome, and others in which single-gene mutations fully explain the pathophysiology of hypertension [34].

2.5.3 Lifestyle Risk Factors

Lifestyle plays a major role in cardiovascular health and has an important effect on blood pressure control. One of the most well-known is salt intake.

2.5.3.1 Salt

The association between salt intake and BP increase has been well established. This finding has been derived from large epidemiological studies [35]. Sodium intake is associated with age-related increase for BP. Moreover excessive salt intake is associated with a higher risk for CVD and stroke [36, 37]. African–Americans, older hypertensive subjects, patients with chronic kidney disease (CKD), diabetes patients, and patients with cardiometabolic syndrome have a higher salt sensitivity. Race and genetics play an important role in salt-sensitive hypertension. Salt sensitivity is especially common in blacks, older adults, and those with a higher level of BP or comorbidities such as CKD, diabetes mellitus, or the metabolic syndrome.

2.5.3.2 Potassium

Prospective studies have demonstrated that potassium intake is inversely related with BP level [38]. The investigators postulated that an increase potassium intake to the recommended level of 90 mmol/day may have the potential to reduce the incidence of hypertension. A meta-analysis of several prospective studies regarding potassium intake showed that higher dietary potassium intake is associated with lower rates of stroke and might also reduce the risk of coronary heart disease and total CVD [39]. These results support recommendations for higher consumption of potassium-rich foods to prevent vascular diseases.

2.5.3.3 Smoking

Smoking will lead to BP rise acutely mainly due to increase of heart rate due to sympathetic activation. A Mendelian randomization meta-analysis was performed by the CARTA consortium including 141,317 participants (62,666 never, 40,669 former, 37,982 current smokers) from 23 population-based studies. They concluded that was a causal association of smoking heaviness with higher level of resting heart rate, but not with blood pressure [40]. These findings suggest that part of the cardiovascular risk of smoking may operate through increasing resting heart rate but not with blood pressure.

2.5.3.4 Alcohol

Several systematic reviews and meta-analyses have shown that alcohol consumption and hypertension are linked in a dose-dependent fashion [41–43]. Alcohol overconsumption is responsible for 36% of the cases of reversible hypertension.

The potential threshold, the dose–response relationship, is not linear over the full range of alcohol consumption, but for both sexes there is a monotonic dose–response relationship for higher levels of consumption, and thus hazardous/harmful drinking and AUDs are closely associated with elevated BP and/or hypertension. The above-described association between hazardous/harmful alcohol consumption and hypertension means that a logical intervention to reduce BP is to reduce alcohol consumption.

2.5.3.5 Obesity

There is an indirect relationship between body mass index and BP with no evidence of a threshold [44, 45]. The relationship with BP is even stronger for waist-to-hip ratio. The relationship between obesity at a young age and change in obesity status over time is strongly related to future risk of hypertension. Becoming normal weight reduced the risk of developing hypertension to a level similar to those who had never been obese [46].

2.5.3.6 Physical Fitness

Epidemiological studies have an inverse relationship between physical activity and physical fitness and level of BP and hypertension [47].

2.5.4 Secondary Hypertension

Secondary causes of hypertension are uncommon and account for 10% of all cases of high BP in an unselected hypertensive population. Although infrequent, secondary forms of hypertension account for many cases of drug-resistant hypertension. Because of this finding, higher prevalence rates of secondary hypertension have been noted in specialized hypertension clinics. Secondary hypertension is usually associated with a specific organ and/or vascular abnormalities, a metabolic abnormality, or endocrine disorder. The diagnosis of these specific hypertensive conditions is important because of the potential for a permanent cure or improvement in control of hypertension. If left undiagnosed, secondary hypertension may lead to progressive target organ damage, as well as CV and renal complications.

In secondary hypertension, the elevated BP may be the major presenting manifestation of an underlying process, or elevated BP may simply be one component of a complex group of signs and symptoms in a patient with a systemic disease. Secondary causes of hypertension are often nonspecific in their presentation, and laboratory test and/or imaging studies are required for screening and confirmation of the diagnosis. Nevertheless, there are some well-recognized clinical presentations and clinical clues which deserve mention and which should raise a clinician's suspicion of a secondary cause of hypertension. The documented early (less than age 30 years) or late (more than age 50 years) onset of hypertension is thought to raise the possibility of secondary form of hypertension. In pediatric populations, congenital renal or endocrine causes of secondary hypertension are more likely to result in elevated BP. Fibromuscular dysplasia of the renal artery(s) characteristically occurs in young white women, generally without a strong family history of hypertension. The most common cause of secondary hypertension in older patients, with associated vascular disease, is atherosclerotic renal artery stenosis. In obese patients, obstructive sleep apnea and Cushing's disease may be considered as potential causes of secondary hypertension. A thorough search for secondary causes of hypertension is not considered cost-effective in most patients with hypertension. Expended work-ups should be considered with compelling clinical or laboratory evidence for a specific secondary cause or when a patient presents with drug-resistant or refractory hypertension or hypertensive crisis and should be referred to a hypertension-specialized clinic. Causes of secondary hypertension are listed in Table 2.2.

Table 2.2 Secondary causes of hypertension

Chronic kidney disease (renal parenchymal disease)
Atherosclerotic renovascular hypertension
Fibromuscular dysplasia
Renal artery aneurysm
Page kidney
Systemic vasculitis
Renin-secreting tumor
Primary hyperaldosteronism
Aldosterone-producing adenoma
Idiopathic hyperaldosteronism
Glucocorticoid-remediable hyperaldosteronism
Pheochromocytoma
Cushing's disease/syndrome
Coarctation of the aorta
Hypothyroidism
Sleep apnea

2.5.5 Chronic Kidney Disease (CKD): Renal Parenchymal Hypertension

CKD or renal parenchymal disease is the most common form of secondary hypertension. Hypertension occurs in more than 80% of patients with chronic renal failure and is a major factor causing their increased CV morbidity and mortality seen in CKD [48]. Any type of CKD, including acute or chronic glomerulonephriti*s*, may be associated with hypertension. Hypertension is frequently the presenting feature of adult polycystic kidney disease. Clinically, affected patients may experience abdominal pain and hematuria, and the renal or associated hepatic cysts may be palpable on physical examination.

CKD should be suspected when the estimated glomerular filtration rate (eGFR) is less than or equal to 60 mL/min/1.73m^2 or when 1+ or greater proteinuria and/or specific urinary sediment abnormalities are noted on urine analysis. The diagnosis can be confirmed either by the direct measurement of glomerular filtration rate (GFR) or collection for a creatinine clearance showing a value of less than 60 mL/min. Proteinuria should be confirmed by a 24-h urine, which should demonstrate a total protein excretion of more than 150 mg or by a spot urine specimen showing microalbuminuria defined as a urine albumin-to-urine creatinine ratio between 30 mg/g and 300 mg/g. In patients with mild or moderate renal insufficiency, stringent BP control is imperative to reduce the progression to end-stage renal disease and reduce the excessive CV risk associated with CKD.

2.5.6 Renovascular Hypertension

Renovascular hypertension may be the most common form of potentially curable hypertension [49]. Current estimates indicate that this is seen in 1–2% of a hypertensive population in general medical practice. There are two major causes, atheromatous disease and fibromuscular dysplasia, of the renal artery, and each is associated with a distinct clinical presentation. Renovascular hypertension frequently is associated with resistance to a multiple drug antihypertensive regimen. It is not surprising, therefore, that up to 30% of patients referred to some specialized hypertension clinics are found to have renovascular hypertension. Several clinical clues occurring alone or in combination may point to the diagnosis of renovascular hypertension:

- New onset or drug-resistant hypertension, before age 30 or after age 50
- Accelerated or malignant hypertension
- Lateralizing epigastric or upper quadrant systolic–diastolic abdominal bruit noted in a hypertensive patient
- Progressive worsening of renal function in response to ACE-I
- Diffuse atherosclerotic vascular disease in the setting of severe hypertension
- Unexplained pulmonary edema (flash pulmonary edema) generally associated with progressive renal insufficiency and occurring during antihypertensive therapy of a renin-dependent hypertension

Other mechanisms can also contribute to the development of progressive hypertension in the setting of renovascular hypertension. Long-standing or accelerated hypertension can promote the development of structural changes such as arteriolar nephrosclerosis in a contralateral kidney in the case of unilateral renal artery stenosis. Associated renal parenchymal damage may also contribute further to BP elevation and renal impairment. The most common cause of renovascular hypertension is atherosclerotic renal artery stenosis, which generally affects the proximal renal arteries. Atherosclerotic renal artery stenosis is progressive and may lead to worsening hypertension, renal artery occlusion, ischemic nephropathy, and renal failure. The majority of these cases with atherosclerotic renal artery disease occur in the setting of other coronary, cerebrovascular, or peripheral vascular disease. Fibromuscular dysplasia of the renal arteries is the most frequent cause of renovascular hypertension in young women (those under 50 years old). This disease occurs rarely in males but may on occasion be seen in males with strong family histories of fibromuscular dysplasia. The clinical suspicion and even the confirmed diagnosis of renovascular hypertension will frequently present clinicians with difficult diagnostic and therapeutic dilemmas. Individualized treatment decisions are currently required for the effective management and treatment of renovascular hypertension. The diagnostic evaluation and therapeutic strategy for patients with suspected renovascular hypertension are predicated on several factors including the severity of hypertension, the presence of associated renal failure or insufficiency, the type of renal artery lesion, the location of the stenotic lesion, the presence of concomitant CVD, a patient's general health status, and the ability of a patient to tolerate multiple antihypertensive medications.

Patients with clinical presentations suggestive of renovascular hypertension can be screened with noninvasive studies (ultrasound), and, if results are positive, confirmation of the diagnosis can be made with renal arteriography. If the index of suspicion for renovascular hypertension is high, renal arteriography can be performed in the absence of noninvasive tests. Noninvasive testing is frequently employed to diagnose or confirm the anatomical site of a renal artery lesion or to examine the functional significance of a renal artery stenosis. Intensive medical therapy for renovascular hypertension is generally required for BP control and involves the use of ACE-Is, in conjunction with multiple other medications. Treatment frequently involves the use of a calcium channel blocker (CCB), judicious use of diuretics, and occasionally the use of a sympathetic inhibitor. Renal

function and serum potassium should be monitored regularly, as they can deteriorate with ACE-I or BP reduction alone. ACE-I should be withdrawn with moderate deterioration (>30%) in renal function and/or if a patient becomes hyperkalemic. Angiotensin receptor blockers (ARBs) should be substituted in those patients who develop an ACE-I cough or those who develop mild hyperkalemia with ACE-I.

Medical management of renovascular hypertension includes intensive treatment of associated CV risk factors, with concomitant aggressive lipid lowering, smoking cessation, and the use of low-dose aspirin. Percutaneous transluminal renal artery angioplasty (PTRA) and stenting or surgical revascularization of the renal arteries should be considered in the setting of drug-resistant and worsening hypertension, in patients who develop progressive renal failure in response to medical therapy, and finally in those with high-grade bilateral renal artery stenosis. Preservation of renal function is currently the leading cited indication for intervention in patients with renal artery stenosis and renovascular hypertension. BP can frequently now be controlled with potent multidrug antihypertensive regimens. Revascularization, however, may prevent renal artery occlusion, progressive ischemic nephropathy, and renal atrophy. Percutaneous and surgical procedures are not without risk. Patient selection and timing may be crucial to limit complications and maximize outcomes.

Several randomized controlled trials (RCT) studied the role of endovascular management of atherosclerotic renal artery stenosis and arterial hypertension, which failed to demonstrate the benefit of stenting. In the largest RCT to date, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study did not find benefit of revascularization compared to medical therapy alone [50]. The current ACC/AHA recommendations for RAS management are supported by many level II evidence cohort studies which consistently found the benefit of revascularization in groups with the highest likelihood of clinically significant RAS [51].

2.5.7 Primary Hyperaldosteronism

Primary hyperaldosteronism or Conn's syndrome is characterized by hypokalemia, hypertension, very low plasma or suppressed renin activity (PRA), and excessive aldosterone secretion [52]. Aldosterone binds with the mineralocorticoid receptor in the distal nephron and contributes to salt and water homeostasis and maintenance of plasma volume through this interaction. Excessive production of the hormone promotes an exaggerated renal Na + –K+ exchange, which usually results in hypokalemia. The diagnosis of primary hyperaldosteronism should be considered in any patient with severe refractory hypertension. Traditionally, it was thought that 1–2% of patients with hypertension had primary hyperaldosteronism. The syndrome has been reported to be more common in females and may present with mild, moderate, or resistant hypertension. Patients are generally asymptomatic, though symptoms such as muscle cramps, weakness, and paresthesias attributable to hypokalemia may predominate. Polyuria and polydipsia have also been reported. Many patients with primary hyperaldosteronism will present with severe, persistent, or refractory diuretic-induced hypokalemia. The best clinical clues to the diagnosis in patients with hypertension is either unprovoked hypokalemia with a serum K+ less than 3.5 mg/dl in the absence of diuretic therapy or the development of more profound hypokalemia during diuretic therapy with a serum K+ less than 3.0 mg/dL. Laboratory testing is frequently required to differentiate between secondary hyperaldosteronism associated with diuretic use, renovascular hypertension, and renin-secreting tumors. The most utilized confirmatory test is the urine aldosterone excretion rate, which involves the 24-h collection of urine, under conditions of a high-salt load. Adrenal computed tomography (CT) scans with 3 mm cuts should be used to localize adenomas or neoplasm. Control of BP and hypokalemia can be obtained with antihypertensive regimens based on spironolactone and eplerenone or, on occasion, with amiloride. Multiple medications will be frequently required. Unilateral adrenalectomy is highly effective for reversing the metabolic consequences of hyperaldosteronism in patients with aldosterone-producing adenoma.

Brown et al. [53] investigated whether a spectrum of subclinical renin-independent aldosteronism increases the risk for hypertension in normotensive persons. They found that suppression of renin and higher aldosterone concentrations in the context of this renin suppression are associated with an increased risk for hypertension and possibly also with increased mineralocorticoid receptor activity. These findings suggest a clinically relevant spectrum of subclinical primary aldosteronism (renin-independent aldosteronism) in normotension.

2.5.8 Pheochromocytoma

Pheochromocytomas are rare catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system. Majority of these tumors are benign and are located in the adrenal gland, but others can develop as functioning paraganglioma in a variety of extra-adrenal sites [54]. Pheochromocytomas generally secrete both norepinephrine and epinephrine, though norepinephrine is usually the predominant amine.

Pheochromocytoma has a reported incidence of 0.05% in the general population with peak incidence occurring in the 30s and 40s. The rule of 10s has been used to characterize the clinical presentation of the tumor: approximately 10% of pheochromocytomas are extra-adrenal, 10% are malignant, 10% are familial, 10% occur in children, 10% are bilateral and affect both adrenals, and 10% are multiple. A family history or an early onset of pheochromocytoma may suggest an

underlying genetic disorder such as multiple endocrine neoplasia type II, Von Hippel–Lindau disease, or neurofibromatosis type I. Classic clinical presentations are characterized by hypertension, palpitations, headache, and hyperhidrosis. The hypertension can be severe and sustained (55%) or paroxysmal (45%). Pounding headaches, palpitations, and diaphoresis are prominent features of the syndrome and may occur together in a paroxysmal attack. Postural hypotension may occasionally be present as a result of low or constricted plasma volume. Hypertension associated with panic attack as well as other causes of neurogenic hypertension, including the BP elevations sometimes seen with sympathomimetic agents, and obstructive sleep apnea can be confused with pheochromocytoma.

Plasma-free metanephrines, if available, are a preferred screening test for excluding or confirming the diagnosis of pheochromocytoma. Twenty-four-hour urine collections for metanephrine (100% sensitive) are also useful for screening for the tumor. The accuracy of the 24-h urine metanephrine may be improved by indexing urinary metanephrine levels by urine creatinine levels. A positive screening test should be reconfirmed if there is a suspicion of drug interference or a false-positive test [55]. Patients with a suspicion of pheocromocytoma should be referred to a specialized center and to emergency in case of a hypertensive crisis.

Table 2.3 Causes of resistant hypertension

Poor adherence to medical regimen
Poor adherence to lifestyle changes
Obesity and weight gain
Heavy alcohol intake
Improper BP measurement
Improper cuff size
Stress or office hypertension
Pseudoresistance in the elderly
Volume overload
Excess sodium intake
Inadequate diuretic therapy
Pseudotolerance
Alpha methyldopa
Direct acting vasodilators
Progressive CKD
Drug-induced or other causes
Inadequate doses of antihypertensive medication
Inappropriate combinations of antihypertensive medications
Drug interactions
Nonsteroidal anti-inflammatory drugs
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives and adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice ingestion
Unsuspected secondary hypertension
Obstructive sleep apnea

2.6 Complicated Management Problems in Hypertension

2.6.1 Resistant Hypertension

Resistant hypertension is becoming an increasingly common problem with the national guidelines focusing on lower goal BPs [56]. The diagnosis of resistant hypertension is made when a patient takes three antihypertensive medications with complementary mechanisms of action (a diuretic should be one of the antihypertensive drugs) but does not achieve control or when BP control is achieved but requires at least four or more medications [57]. With the new definition of hypertension (target BP <130/80 mmHg), one may expect a higher incidence of resistant hypertension.

True drug-resistant hypertension is relatively rare, but treatment failure is relatively common, frequently being secondary to nonadherence, socioeconomic factors, and lifestyle issues. Before embarking on an expanded work-up to determine the cause of drug-resistant hypertension, clinicians should be careful to rule out "pseudoresistance" secondary to BP measurement artifacts or errors and "white-coat" hypertension and antihypertensive medication compliance. Out-of-office measurements, including home BPs, or 24-h ambulatory BP monitoring (ABPM) may be required to establish a patient's actual BP. The absence of target organ damage in the setting of prolonged resistant or refractory hypertension should raise a clinician's suspicion regarding pseudoresistance.

Refractory hypertension is an extreme phenotype of antihypertensive treatment failure, defined as uncontrolled blood pressure (systolic/diastolic, ≥140/90 mm Hg) on ≥5 antihypertensive drug classes [58]. Participants with resistant hypertension are older and commonly present with obesity, unrestricted or excessive dietary salt intake, and the clinical syndrome of sleep apnea. Causes of resistant hypertension are summarized in Table 2.3.

Current approaches to correction of drug resistance focus on evaluation and correction of potential contributing causes, the development of a more effective drug regimen, and identification of any unrecognized secondary causes of hypertension.

Volume expansion plays a key role in drug resistance, and it cannot be adequately assessed with a clinical exam. Treatment should include a strong emphasis on lifestyle changes including weight loss, exercise, dietary, and salt restriction, all of which should be monitored. New multidrug antihypertensive regimens should incorporate the more potent vasodilator antihypertensive agents such a CCBs or direct acting vasodilators with adequate diuretic therapy, especially if intense vasoconstriction is suspected as the physiologic cause or culprit. Recent data indicate that

aldosterone antagonists may be effective when added to existing antihypertensive regimens even in the absence of primary aldosteronism [59]. Consultation with a hypertension specialist should be considered if target BP cannot be achieved.

2.6.2 Hypertensive Emergencies and Urgencies

Hypertensive emergencies are defined as severe elevations in BP (>180/120 mm Hg) associated with evidence of new or worsening target organ damage. It is very important that in case of hypertensive emergencies, one starts to lower immediately the SBP and DBP. Hypertensive urgencies are situations associated with severe BP elevation in otherwise stable patients without acute or impending change in target organ damage or dysfunction. Following the 2017 ACC/AHA new hypertension guidelines, in adults with a compelling condition (i.e., aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to less than 140 mm Hg during the first hour and to less than 120 mm Hg in aortic dissection ([3]; see original Fig. 11).

For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hour and then, if stable, to 160/100 mm Hg within the next 2–6 h and then cautiously to normal during the following 24–48 h [3].

The presence of severe hypertension alone is not sufficient to make the diagnosis of hypertensive emergency. The diagnosis of hypertensive emergencies ultimately depends on the clinical presentation rather than on the absolute level of the BP. Thus, these cases usually present with severe hypertension complicated by some cardiac, renal, neurologic, hemorrhagic, or obstetric manifestation. Hypertensive encephalopathy, acute aortic dissection, and pheochromocytoma crisis are well-recognized hypertensive emergencies. Some cases of accelerated or malignant hypertension, acute left ventricular failure, cerebral infarction, head injury, scleroderma, and acute myocardial infarction interaction can also present as hypertensive emergencies. Other causes for an acute symptomatic rise in BP include medications, noncompliance, and poorly controlled chronic hypertension.

The clinical history and physical examination should be highly focused in an attempt to determine the cause of a patient's severe hypertension and should attempt to exclude other clinical presentations which may mimic hypertensive emergencies or urgencies such as panic attack or postictal hypertension.

There is no randomized controlled trial (RCT) evidence that antihypertensive drugs reduce morbidity or mortality in patients with hypertensive emergencies. There is also no high-quality RCT evidence to inform clinicians as to which first-line antihypertensive drug class provides more benefit than harm in hypertensive emergencies. This lack of evidence is related to the small size of trials, the lack of long-term follow-up, and failure to report outcomes. Several antihypertensive agents in various pharmacological classes are available for the treatment of hypertensive emergencies.

2.7 Blood Pressure Measurement

2.7.1 Office Blood Pressure Measurement

The most common reason for an outpatient physician visit is for the diagnosis and treatment of hypertension. Standardized BP measurement is the basis for the diagnosis, management, treatment, epidemiology, and research of hypertension, and the decisions affecting these aspects of hypertension will be influenced, for better or worse, by the accuracy of measurement [60]. Accurate BP measurement is well described in the new hypertension guidelines [3]. All of these guidelines are a synthesis of the methodology used in all the important epidemiologic and treatment trials of hypertension. Factors important in this methodology include (i) resting for 5 min, (ii) sitting with back supported and feet on the floor, (iii) arm supported at heart level, (iv) appropriate size cuff applied, (v) use of the Korotkoff Phase I sound for SBP and Phase V for DBP, and (vi) using the mean of two or more BP measurements as the patient's BP. Failure to conform to all of these recommendations can result in significant errors in ausculted BP and misdiagnosis and mistreatment of the hypertensive patient. Certain groups of people merit special consideration for BP measurement.

These include children; the elderly, who often have isolated systolic hypertension or autonomic failure with postural hypotension; obese people in whom the inflatable bladder may be too small for the arm size, leading to "cuff hypertension"; patients with arrhythmias in whom BP measurement may be difficult and the mean of a number of measurements may have to be estimated; pregnant women in whom the disappearance of sounds (Phase V) is the most accurate measurement of diastolic pressure, except when sounds persist to zero, when the fourth phase of muffling of sounds should be used; and any individual during exercise.

Bilateral measurements should be made on first consultation, and, if persistent differences greater than 20 mmHg for systolic or 10 mmHg for diastolic pressure are present on consecutive readings, the patient should be referred to a CV center for further evaluation with simultaneous bilateral measurement and the exclusion of arterial disease.

The second option for accurate BP measurement is the use of validated automated BP devices. The automated BP-measuring devices use a proprietary oscillometric method. Each of these devices needs to be independently validated and then calibrated to each patient. Rarely, they do

not sense BP accurately but, more commonly, fail if the cardiac rhythm is very irregular (e.g., atrial fibrillation). It is interesting to note that even with auscultatory BP measurement in elderly patients with atrial fibrillation, considerable observer variability is seen. It is critically important that if an automated BP-measuring device is used, it must have passed a recognized validation protocol.

2.7.2 Home BP Measurement

Home BP monitoring has become popular in clinical practice, and several automated devices for home BP measurement are now recommendable. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. Home BP is generally lower than clinic BP and similar to daytime ambulatory BP. Home BP measurement eliminates the white-coat effect and provides a high number of readings, and it is considered more accurate and reproducible than clinic BP. It can improve the sensitivity and statistical power of clinical drug trials and may have a higher prognostic value than clinic BP. Home monitoring may improve compliance and BP control and reduce costs of hypertension management. Diagnostic thresholds and treatment target values for home BP remain to be established by longitudinal studies. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions [61]. Until then, home BP monitoring is to be considered a supplement. Home BP provides an opportunity for additional monitoring of BP levels and its variability.

Some advantages of self-measured BP are raising patient awareness of how their BP responds to medication or dietary changes, decreasing physician inertia to adjust medication when the office-measured BP is high, and decreasing office visits for BP management. Adequate self-measurement of BP is more associated with target organ damage than office-based BP, and its prognostic value is comparable with ambulatory BP recording based on observational studies.

2.7.3 Ambulatory BP

Ambulatory blood pressure (ABPM) provides automated measurements of brachial artery blood pressure over a 24-h period, while patients are engaging in their usual activities. This method has been used for more than 30 years in clinical research on hypertension [62–64]. These studies demonstrated that BP has a highly reproducible circadian profile, with higher values when the patient is awake and mentally and physically active, much lower values during rest and sleep, and an early morning surge lasting 3–5 h during the transition from sleep to wakefulness. In a patient with hypertension, 24-h BP monitoring has substantial appeal. It yields multiple BP readings during all of the patient's activities, including sleep, and gives a far better representation of the "BP burden" than what might be obtained in a few minutes in the doctor's office. Several prospective clinical studies, as well as population-based studies, have indicated that the incidence of CV events is predicted by BP as measured conventionally or with ambulatory methods, even after adjustment for a number of established risk factors [63, 64].

In clinical practice, measurements are usually made at 20–30-min intervals in order not to interfere with activity during the day and with sleep at night. Measurements can be made more frequently when indicated. Whatever definition of daytime and nighttime is used, at least two-thirds of SBPs and DBPs during the daytime and nighttime periods should be acceptable. If this minimum requirement is not met, the ABPM should be repeated. A diary card may be used to record symptoms and events that may influence ABPM measurements, in addition to the time of drug ingestion, meals, and going to and arising from bed. If there are sufficient measurements, editing is not necessary for calculating average 24-h, daytime, and nighttime values, and only grossly incorrect readings should be deleted from the recording. Table 2.4 summarizes the corresponding values of SBP/DBP for clinic, home BP measurement, and daytime, nighttime, and 24-hr ABPM.

ABPM has a number of advantages: it provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white-coat response; it shows BP behavior over a 24-h period during usual daily activities, rather than when the individual is sitting in the artificial circumstances of a clinic or office. It can indicate the duration of decreased BP over a 24-h period. ABPM can identify patients with blunted or absent BP reduction at night—the nondippers—who are at greater risk for organ damage and CV morbidity. It can demonstrate a number of patterns of BP behavior that may be relevant to clinical management, such as white-coat hypertension and masked hypertension.

Table 2.4 Corresponding values of SBP/DBP for clinic, HBPM, daytime, nighttime, and 24-h ABPM measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

Adapted Table 11 from Whelton et al. [3]
ABPM indicates ambulatory blood pressure monitoring, *BP* blood pressure, *DBP* diastolic blood pressure, *HBPM* home blood pressure monitoring, and *SBP* systolic blood pressure

The recent 2017 ACC/AHA guidelines for hypertension recommend the following measurements for masked or white hypertension [3]:

- In adults with an untreated SBP greater than 130 mm Hg but less than 160 mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is reasonable to screen for the presence of white-coat hypertension by using either daytime ABPM or home BP measurement before diagnosis of hypertension.
- In adults with white-coat hypertension, periodic monitoring with either ABPM or home BP measurement is reasonable to detect transition to sustained hypertension.
- In adults being treated for hypertension with office BP readings not at goal and home BP measurement readings suggestive of a significant white-coat effect, confirmation by ABPM can be useful.
- In adults with untreated office BPs that are consistently between 120 mm Hg and 129 mm Hg for SBP or between 75 mm Hg and 79 mm Hg for DBP, screening for masked hypertension with HBPM (or ABPM) is reasonable.
- In adults on multiple-drug therapies for hypertension and office BPs within 10 mm Hg above goal, it may be reasonable to screen for white-coat effect with HBPM or ABPM.
- It may be reasonable to screen for masked uncontrolled hypertension with HBPM in adults being treated for hypertension and office readings at goal, in the presence of target organ damage or increased overall CVD risk.
- In adults being treated for hypertension with elevated HBPM readings suggestive of masked uncontrolled hypertension, confirmation of the diagnosis by ABPM might be reasonable before intensification of antihypertensive drug treatment.

2.8 Evaluation of Hypertension

Following the confirmation of hypertension, a targeted history and physical examination and limited laboratory evaluation should be performed. The standard hypertensive work-up includes an assessment of CV risk and the identification of hypertensive target organ damage and is designed to rule out secondary hypertension. This examination should include information regarding a patient's habits and lifestyle, which could contribute to his or her hypertension.

The identification of other CV risk factors or concomitant disorders may affect prognosis and guide treatment. The major CV risk factors and types of hypertension-associated target organ damage are listed in Table 2.5. The medical history and physical examination are also the most important components of a pretreatment evaluation in the differentiating detailed questioning which focuses on obtaining the following medical information:

Table 2.5 Cardiovascular risk factors

Major risk factors
Hypertension
Cigarette smoking
Obesity (BMI >30 kg/m^2)
Physical inactivity
Dyslipidemia
Diabetes mellitus
Microalbuminuria or estimated GFR (glomerular filtration rate) <60 mL/min
Age (>55 years for men, >65 years for women)
Family history of premature CVD (men <55 years or women 65 years)
Target organ damage
Left ventricular hypertrophy
Angina or prior myocardial infarction
Coronary atherosclerosis
Prior coronary revascularization
Heart failure
Mild cognitive impairment
Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

- Family history of hypertension
- Family history of premature CVD, diabetes, or dyslipidemia
- Estimated duration of hypertension, current and previous hypertension stage, and drug therapy
- Home BP measurements
- Medical history, clinical signs, and symptoms of CV or renal disease
- Medical history, clinical signs, and symptoms of comorbid disease, which may affect selection of drug therapy [asthma, chronic obstructive pulmonary disease (COPD)
- Complete medication history including prescription, over-the-counter (OTC) medications, herbal remedies, and drug allergies
- History of drug and alcohol abuse

The importance of the medication history cannot be overemphasized. A variety of drugs can elevate BP and interfere with the effect of antihypertensive medications.

Corticosteroids, cyclosporine, tacrolimus, and oral contraceptives are well-recognized causes of BP elevation. Ephedrine, sympathomimetics, and amphetamine-like agents, available in OTC cough and sinus preparations, can increase peripheral resistance and interfere with BP control. Commonly used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) can also cause hypertension or interfere with the effect of a variety of antihypertensive medications.

The initial physical examination should include the following:

- Vital signs, including body mass index (BMI)
- Sitting and standing BP and heart rates
- BP measurement in the contralateral arm
- Examination of the optic fundi, neck, heart, lungs, and abdomen
- Auscultation of the neck and abdomen for bruits
- Palpation of peripheral pulses and extremity check for edema
- Neurological examination

A limited laboratory evaluation is recommended at the time of initial diagnosis. This should include a complete blood count, chemistry (including Na, K, Ca, glucose, and uric acid), a complete lipid profile, and urinalysis. Recent trends have focused on better baseline assessment of renal function in hypertensive patients. Although not mandatory in most hypertensive patients, a measurement of urinary albumin excretion or albumin/creatinine ratio may be useful in diagnosing renal disease or establishing future CV risk. A positive result could affect the intensity and type of antihypertensive therapy. Many reference laboratories now routinely calculate the estimated glomerular filtration rate (eGFR), which can be used to identify or exclude CKD (chronic kidney disease) or to monitor the effect of antihypertensive therapy on renal function.

Additional laboratory and imaging tests may be required to quantify CV risk, to characterize target organ damage, or to screen for secondary hypertension in some complicated patients. Given the high frequency of additional CV risk factors in hypertension, clinicians may want to use a risk assessment tool for determining a patient's 10-year or lifetime risk for developing coronary heart disease (CHD). Such risk assessments may be useful for estimating global CV risk and in modifying patient behavior.

2.9 Treatment

2.9.1 Nonpharmacological Therapy

The stated goal for the treatment of hypertension is to prevent CV morbidity and mortality associated with high BP. Such a goal now requires the treatment of all identified reversible risk factors accompanying hypertension to maximize CV event reduction. The basics of nonpharmacological therapy are a cardiovascular healthy diet and reducing salt intake, regular physical activity, reduction in excessive alcohol consumption, and stop smoking [3]. Nonpharmacological therapy alone is especially useful for prevention of hypertension, including adults with elevated BP, and for management of high BP in adults with milder forms of hypertension. Following recommendations were formulated in the 2017 ACC/AHA guidelines [3]:

1. Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese [65].
2. A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension [66].
3. Sodium reduction is recommended for adults with elevated BP or hypertension [67].
4. Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion [68].
5. Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension [69].
6. Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than two and one standard drinks per day, respectively [70].

2.9.2 Pharmacological Therapy

In the 2017 ACC/AHA guidelines for the medical treatment of hypertension, the major focus on lowering BP is not only lowering the number but targeting a BP goal within the global CVD risk of the hypertensive patient in order to obtain a maximal CVD risk reduction in which two different BP thresholds are considered:

1. The use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher [1, 3, 5–8, 71].
2. The use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and a SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher [1].

The 2017 ACC/AHA hypertension guidelines recommend the following for follow-up after initial BP evaluation:

1. Adults with an elevated BP or stage 1 hypertension who have an estimated 10-year ASCVD risk less than 10% should be managed with nonpharmacological therapy

and have a repeat BP evaluation within 3–6 months [3, 72, 73].
2. Adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of 10% or higher should be managed initially with a combination of nonpharmacological and antihypertensive drug therapy and have a repeat BP evaluation in 1 month [3, 72, 73].
3. Adults with stage 2 hypertension should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacological and antihypertensive drug therapy (with two agents of different classes) initiated, and have a repeat BP evaluation in 1 month [3, 72, 73].
4. For adults with a very high average BP (e.g., SBP ≥180 mm Hg or DBP ≥110 mm Hg), evaluation followed by prompt antihypertensive drug treatment is recommended [3, 72, 73].
5. For adults with a normal BP, repeat evaluation every year is reasonable.

Despite BP-lowering medication, the main goal of antihypertensive medication is to reduce the risk of CVD, cerebrovascular events, and death [4–7]. The primary antihypertensive agents to be used are the primary agents used in the treatment of hypertension which include thiazide diuretics, ACE inhibitors, ARBs, and CCBs [8–11]. There is no evidence to support the initial use of beta-blockers for hypertension in the absence of specific cardiovascular comorbidities (post-myocardial infarction, angina, presence of coronary artery disease). There is also no evidence to combine an angiotensin-converting enzyme inhibitor (ACE-I) and an angiotensin II receptor blocker (ARB) because the risk outweighs the benefit. The longtime dilemma was starting with one single antihypertensive agent or initially already starting with a combination of antihypertensive therapy. Other patient-specific factors, such as age, concurrent medications, drug adherence, drug interactions, the overall treatment regimen, out-of-pocket costs, and comorbidities, should be considered to obtain a maximal patient compliance and BP control. A combination therapy of two antihypertensive drugs will lower BP by acting on two different mechanisms which has a certain advantage instead of going to the maximum dosage on one antihypertensive drug and then adding another one if BP is still not achieved. Moreover the combination therapy can be administered in a lower dose of the two different antihypertensive drugs and consequently will lead to less side effects.

2.10 Classes of Antihypertensive Medication

Table 2.6 summarizes the primary and the secondary classes of antihypertensive drugs. It is a summary of Table 18 from the 2017 ACC/AHA hypertension guidelines in which the different classes of antihypertensive drugs are described in

Table 2.6 Primary and secondary blood pressure-lowering agents

Primary BP-lowering agents		
Diuretics		
Thiazide or thiazide-type diuretics: Chlorthalidone preferred based on prolonged half-life and CVD reduction monitor Na, K, Ca, and uric acid – caution in case of history of gout		
ACE-inhibitors: Not in combination with ARB or DRI Check renal function and K No use in case of history of angioedema Risk for renal insufficiency in case of bilateral renal artery stenosis Avoid in pregnancy		
ARB: Not in combination with ACE-I or DRI Check renal function and K No use in case of history of angioedema Risk for renal insufficiency Avoid in pregnancy		
CCB		
Dihydropyridines	Avoid in HFrEF	
	Peripheral edema more in women than in men	
	Administer preferentially in the evening to avoid peripheral leg edema	
Non-dihydropyridines		
	Avoid combination with BB	
	Do not use it in HFrEF	
	CYP3AR	pharmacological interaction
Secondary BP-lowering agents		
Diuretics		
Loop diuretics:	Preferred diuretics in hypertension in moderate to severe CKD	
Potassium sparing diuretics:	In combination with HCTZ	
Mineralocorticoid receptor antagonist (MRA)	resistant HTN, adrenal hyperplasia	
	Hypertension and HFpEF	
	Potassium-sparing	
Beta-blockers	Avoid abrupt cessation	Avoid in reactive airway disease
	Not recommended as first line except in ischemic heart disease or HF	
Non-selective		
Cardioselective	Preferential if indicated to use as antiHTN drug	
BB with alpha-blocking effects	Carvedilol preferential for HF	
BB with ISA	Avoid in IHD and HF	
BB cardioselective and vasodilatory:	Induces NO-induced vasodilation	
Alpha-1 blocker:	Orthostatic hypotension	
	Second line in case of BPH	
Central alpha-1 agonist and other centrally acting drugs		
	Last line antiHTN drug	
	Risk abrupt clonidine withdrawal and BP rise	
Direct vasodilators: Sodium and water retention and reflex tachycardia		
Direct renin inhibitor: Not in combination with ACE-I and ARB		
	Limited use as antiHTN	

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blockers, *DRI* direct renin inhibitors, *CCB* calcium channel blockers, *HFrEF* heart failure with reduced ejection fraction, *BB* beta-blocker, *CKD* chronic kidney disease, *HCTZ* hydrochlorothiazide, *NO* nitric oxide

detail regarding the doses of the individual antihypertensive drug and the preferential indication, the side effects, and the avoidance of combining some of the two classes [3]. The most important point regarding the new guidelines is that the beta-blockers are considered not anymore as first-line antihypertensive drugs but as secondary except if the hypertensive patient has ischemic heart disease or myocardial infarction.

Once antihypertensive therapy has been started, the clinical follow-up evaluation should include assessment of BP control, as well as evaluation for orthostatic hypotension, adverse effects from medication therapy, adherence to medication and lifestyle therapy, need for adjustment of medication dosage, laboratory testing (including electrolyte and renal function status), and other assessments of target organ damage. In order to improve better BP control, home BP is recommended [74].

2.11 Hypertension in Patients with Comorbidities

Arterial hypertension is often diagnosed when patient consults for another problem and is newly diagnosed with diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, and peripheral arterial disease. The patient may be admitted for a stroke, acute heart failure, and acute myocardial infarction. These comorbidities will determine and affect the decision-making regarding the treatment of hypertension as well the choice of the antihypertensive drugs.

The 2017 ACC/AHA guidelines have made several recommendations for these hypertensive patients with comorbidities [3]:

2.11.1 Stable Ischemic Heart Disease

1. In adults with stable ischemic heart disease and hypertension, a BP target of less than 130/80 mm Hg is recommended.
2. Adults with stable ischemic heart disease and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., beta-blockers, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension.
3. In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to beta-blockers is recommended.
4. In adults who have had an MI or acute coronary syndrome, it is reasonable to continue beta-blockers beyond 3 years as long-term therapy for hypertension.
5. Beta-blockers and/or CCBs might be considered to control hypertension in patients with CAD (without HFrEF) who had an MI more than 3 years ago and have angina.

2.11.2 Heart Failure

Treatment of hypertension with heart failure is incorporated in the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure [75].

2.11.3 Chronic Kidney Disease

The 2017 ACC/AHA recommendations for treatment of hypertension in patients with CKD are [3]:

1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.
2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d or ≥ 300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.
3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d or ≥ 300 mg/g albumin-to-creatinine ratio in the first morning void]), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

2.11.4 Stroke Prevention

Treatment of hypertension and cerebral hemorrhage and acute stroke and secondary stroke prevention are summarized in the new 2017 ACC/AHA hypertension guidelines based on outcome trials [3].

2.12 Diabetes

Nearly 80% of patients with diabetes have hypertension. The 2017 ACC/AHA guidelines committee made three recommendations [3]:

1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.

2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

2.13 Race and Ethnicity

Lifestyle is here priority, but socioeconomic factors play an important role in the success of healthy lifestyle. The 2017 ACC/AHA made the following recommendations:

1. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
2. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.

2.14 Pregnancy

1. Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy [3].
2. Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors [3].

2.15 Elderly

1. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher [3].
2. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs [3].

2.16 New Developments in BP Monitoring and Antihypertensive Treatment

During the last decade, efforts are made in a better BP monitoring outside the clinic.

The focus in the development of new BP-lowering therapy has mainly focused in resistant hypertension with the emphasis of renal nerve denervation and carotid baroreceptor stimulation [29]. Renal nerve denervation did not fulfill the expectations, but research in newer techniques and more focused hypertensive patients is ongoing. Endothelin antagonists are still studied, and new mineralocorticoid receptor antagonists are studied.

2.17 Conclusions

Arterial hypertension is the most common and modifiable cardiovascular risk factor in the world. The new 2017 ACC/AHA guidelines have altered the standard target BP for decades from 140/90 mmHg to a target goal of 130/90 mmHg and incorporated it in a more CVD risk approach. A healthy lifestyle is still the absolute priority. Antihypertensive drugs have now been considered in a primary class, and HCTZ, ACE-I, ARB, CCBs, and the beta-blockers have been moved to the secondary class. Despite tremendous effort over the years, still more effort needs to be done for early detection and treatment of hypertension. Data obtained from epidemiological studies provided information that based on the current approach, antihypertensive treatment cannot restore cardiovascular disease risk to ideal levels [76]. Moreover, the TROPHY study provided us the evidence that due to pharmacological treatment with an ARB, development of hypertension could be delayed in time [77]. Another fact cannot be ignored; we still treat hypertension based on systolic and diastolic BP, which are the two extreme points of the BP waveform. A more thorough noninvasive blood pressure waveform helps us to provide more precision on how to maintain vascular health [78].

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