2 Arterial Hypertension

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CONTENTS

Key Words: Angiotensin; Beta-blocker; Blood pressure; Isolated systolic hypertension; Hypertensive nephropathy.

KEY POINTS

- High blood pressure is one of the most important cardiovascular risk factors.
- The general cutpoint for hypertension is 140/90 mmHg.
- In diabetes mellitus and chronic kidney disease, the BP goal should be lower than 130/80 mmHg.
- Prehypertension is a cardiovascular risk factor.
- The pathogenesis of essential hypertension is a heterogeneous process and several systems are involved in the changes of cardiovascular hemodynamics.

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- In more than 90% of patients, elevated blood pressure is due to essential hypertension, in which genetic and environmental factors are involved.
- Interpretation of blood pressure values is dependent on whether they are measured in the office, at home, or during a 24-h ambulatory BP recording.
- In the evaluation of hypertension, other risk factors have to be taken into consideration.
- Treatment of hypertension is not only lowering blood pressure but the main aim is to reduce the risk for CV morbidity and mortality as well to preserve renal function.
- Antihypertensive treatment should be focused on lifestyle changes and personalized blood pressure lowering therapy in the context of other concomitant morbid conditions.
- Several landmark trials have shown that there can be a difference in cardiovascular and renal outcome, depending on how blood pressure is lowered.
- Age is not a contraindication to lowering blood pressure.

2.1. INTRODUCTION

High blood pressure (BP) is a very important cardiovascular (CV) risk factor and is often labeled the "silent killer" because arterial hypertension will lead to serious CV events such as ischemic heart disease, stroke, and heart failure. Moreover, uncontrolled essential hypertension also leads to renal insufficiency, which accelerates the process of blood pressure elevation *(1*, *2)*. 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.

2.2. DEFINITION

Hypertension is now defined on the basis of systolic (SBP) and diastolic (DBP) blood pressure levels and classified into stages on the basis of the degree of elevation. The generally recognized cutpoint for hypertension is an average office BP of 140/90 mmHg or greater, which has been obtained by a recommended standard technique with an accurate manometer and has been confirmed on at least one other occasion. This general definition has been modified for the classification of hypertension in specific high-risk populations such as diabetes mellitus and chronic kidney disease (CKD).

Throughout middle and old age, BP is strongly and directly related to vascular and overall mortality, without any evidence of a threshold down to at least 115/75 mmHg. Normal BP is widely considered to being less than 120/80 mmHg. Alternate definitions for hypertension exist for BP measurements made with home BP and ambulatory BP monitoring. Home BPs of more than 135/85 mmHg generally correlate well with office BPs of 140/90 mmHg or greater. Awake ambulatory BPs of more than 140/90 mmHg and sleep averaged BPs of more than 125/75 mmHg are now considered to be sufficient for the diagnosis of hypertension. Although pulse pressure (PP), the difference between SBP and DBP in mmHg, has been used to characterize CV risk in hypertension, it does not yet contribute to the definition of the hypertensive status.

Prehypertension is now considered to be a CV risk factor *(3)*. It is defined as an SBP between 120 and 139 mmHg systolic and a DBP of 80–89 mmHg. These subjects are at very high risk to develop arterial hypertension.

2.3. EPIDEMIOLOGY OF HYPERTENSION

Hypertension is considered to be the most common reversible or treatable CV risk factor. When defined as a BP of 140/90 mmHg, it affects 50 million residents of the United States, with an estimated one billion people worldwide. 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 that accounts for a substantial portion of total global disease burden *(4)*. From a clinical perspective, there is one generally accepted cardinal principle that describes the hypertensive state and that has served to define the importance of hypertension to world health. The presence of an elevated uncontrolled BP over time will lead to progression in the severity or stage of hypertension, the development or worsening of target organ damage, and 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. This relationship between SBP and DBP elevation and CVD mortality is best described by the Prospective Studies Collaboration, a meta-analysis that found 120,000 deaths among one million participants in 61 cohorts *(4)*. Individuals with preexisting vascular disease were excluded from this meta-analysis. During 12.7 million person-years at risk, there were about 56,000 vascular deaths (12,000 strokes, 34,000 ischemic heart disease, 10,000 other vascular) that occurred in adults between 40 and 89 years of age. Throughout middle age, as BP increases, each difference of 20 mmHg in the usual SBP (usual BP at the start of each decade) and/or approximately equivalent 1 mmHg usual difference in DBP was associated with a more than twofold increase in the stroke death rate. Because stroke is much more common in old age than in middle age, the absolute annual differences in stroke death associated with a given BP difference were greater in old patients. In addition, each 20 mmHg difference in usual SBP was associated with a twofold difference in the death rate from ischemic heart disease. All of the proportional differences found in vascular mortality were reduced by half in the 80–89 year age group. Age-specific associations for men and women were similar. Perhaps the most striking finding of this meta-analysis was that relatively small reductions in mean SBP would be associated with large absolute reductions in premature deaths and disabling strokes. Thus a 2-mmHg lower mean SBP could lead to a 7% lower risk of ischemic heart disease death and a 10% lower risk of stroke death. Unfortunately, a gap continues to exist between hypertension and awareness and control worldwide *(5)*.

2.4. MECHANISMS OF HYPERTENSION

The pathogenesis of essential hypertension is a heterogeneous process and involves several systems resulting in altered 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 *(6)*. In recent years there has been more attention devoted to pulse pressure, which is the difference between SBP and DBP and is a simple parameter conferring information about arterial stiffness *(7)*.

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. 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 and the renin–angiotensin–aldosterone system (RAAS), endothelial dysfunction, electrolyte changes, and alterations in the release of endothelial relaxing factor.

2.4.2. Renal

The relationship between the development or pathogenesis of hypertension and the kidney is complex. The kidney, through a variety of distinct mechanisms, can cause or contribute to the development and progression of hypertension. 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. These mechanisms most certainly contribute to the BP elevation, which accompanies CKD and some cases of primary hypertension *(8)*. 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 *(9)*. 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. 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.

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.

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. 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 *(10)*.

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, 93–95% of hypertensives have no known

cause for their hypertension. For that reason, most hypertension states were originally classified as "essential" hypertension.

2.5.1. Essential or Primary Hypertension

Although the pathogenesis of essential or primary hypertension is uncertain, as previously noted, specific mechanisms appear to be involved in the development of primary hypertension: altered regulation of the sympathetic nervous system, abnormalities of the renin–angiotensin–aldosterone system, 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. Thus, the etiology of primary hypertension is very complex and includes a mosaic of interrelated factors, which may affect total peripheral resistance and result in the development of primary hypertension. Irrespective of the exact etiologic mechanisms whereby patients develop hypertension, most patients seem to progress along a similar hemodynamic cascade, which involves an early increase in cardiac output, followed by a subsequent rise in total peripheral resistance.

There still, however, is a possibility that our concept of primary hypertension is flawed and that we are dealing with multiple distinct clinical syndromes. The majority of patients who develop primary hypertension do so between 20 and 50 years of age. Most cases are diagnosed as part of routine examinations and generally in the absence of overt target organ damage at initial presentation.

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 signs or symptoms, 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. Secondary Hypertension

Secondary causes of hypertension are uncommon and account for less than 5% of all cases of high BP in unselected hypertensive populations. Although infrequent, secondary forms of hypertension account for many cases of drug-resistant hypertension. As a result of this finding, higher prevalence rates of secondary hypertension have been noted in specialized hypertension clinics. Secondary hypertension is usually associated with 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 tests and/or imaging studies are required for screening and confirmation of the diagnosis. Nevertheless, there are some well-recognized clinical presentations and clinical clues that deserve mention and that 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 forms 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 should 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. Expanded workups 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 specialty clinic. Causes of secondary hypertension are listed in Table 1.

Table 1
Secondary Causes of Hypertension

Chronic kidney disease (renal parenchymal disease)
Renovascular hypertension
Atherosclerosis
Fibromuscular dysplasia
Renal artery aneurysm
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

2.5.3. 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. Any type of CKD, including acute or chronic glomerulonephritis, 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 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 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 to reduce the excessive CV risk associated with CKD.

2.5.4. Renovascular Hypertension

Renovascular hypertension may be the most common form of potentially curable hypertension *(11)*. Current estimates indicate that 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 is frequently 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:

1. New-onset or drug-resistant hypertension before age 30 or after age 50
2. Accelerated or malignant hypertension
3. Lateralizing epigastric or upper quadrant systolic–diastolic abdominal bruit noted in a hypertensive patient
4. Progressive worsening of renal function in response to an ACE-inhibitor
5. Diffuse atherosclerotic vascular disease in the setting of severe hypertension
6. Unexplained pulmonary edema (flash pulmonary edema) generally associated with progressive renal insufficiency and occurring during antihypertensive therapy for 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 is 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, 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 an ACE-inhibitor, 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 inhibition or BP reduction alone. ACE-inhibitors 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 inhibition.

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 renal artery angioplasty 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 now be frequently 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 to maximize outcomes.

2.5.5. 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 *(12)*. 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 mmol/L in the absence of diuretic therapy, or the development of more profound hypokalemia during diuretic therapy with a serum K^+ less than 3.0 mmol/L. 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, 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.

2.5.6. Pheochromocytoma

Pheochromocytomas are rare catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system. The majority of these tumors are benign and are located in the adrenal gland, but others can develop as functioning paragangliomas in a variety of extra-adrenal sites. Pheochromocytomas generally secrete both norepinephrine and epinephrine, though norepinephrine is usually the predominant amine *(13)*.

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 attacks 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. Patients with a suspicion of pheochromocytoma should be referred to a specialized center and to emergency rooms in case of a hypertensive crisis.

2.6. COMPLICATED MANAGEMENT PROBLEMS IN HYPERTENSION

2.6.1. Resistant Hypertension

Resistant hypertension or "hard-to-treat" hypertension is becoming an increasingly common problem with the national guidelines focusing on lower goal BPs *(14)*. True drug-resistant hypertension is relatively rare, but treatment failure is relatively common, frequently being secondary to nonadherence, socioeconomic factors, and lifestyle issues. Resistant hypertension is generally defined as the failure to achieve a therapeutic target of less than 140/90 mmHg in most hypertensive patients, or less than 130/80 mmHg in diabetics or patients with CKD on a well-designed three-drug antihypertensive medical regimen combined with intensive lifestyle modification. In most cases, resistant hypertension is now defined on the basis of a persistently high SBP level. Before embarking on an expanded workup 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. 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. Patients with resistant hypertension are older and commonly present with obesity, unrestricted or excessive dietary salt intake, and the clinical syndrome of sleep apnea. Common causes of resistant hypertension are summarized in Table 2.

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 identifying 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 as calcium channel blockers (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 aldosterone *(15)*. Consultation with a hypertension specialist should be considered if target BP cannot be achieved.

2.6.2. Hypertensive Emergencies and Urgencies

Hypertensive emergencies and urgencies present infrequently in medical practice. When they do occur, they require prompt evaluation and intervention. A hypertensive emergency can be defined as

Table 2
Causes of Resistant Hypertension

Poor adherence to medical regimen
Improper BP measurement
Improper cuff size
Poor adherence to lifestyle changes
Obesity and weight gain
Heavy alcohol intake
Stress or office hypertension
Pseudoresistance in the elderly
Volume overload
Excess sodium intake
Pseudotolerance
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, adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice ingestion
Unsuspected secondary hypertension
Sleep apnea

a sudden and/or severe elevation in BP that causes or contributes to pathologic disturbances in the central nervous system, the heart, the vascular system, or the kidneys, and that requires prompt BP reduction in order to maintain the integrity of the CV system.

Hypertensive emergencies are true medical emergencies that require prompt recognition and thoughtful management in order to reduce the morbidity and mortality associated with severe hypertension. BP reduction typically is begun within minutes to hours of diagnosis and is frequently required to prevent worsening of an underlying clinical condition *(16)*.

The term "hypertensive urgency" refers to a clinical presentation of severe hypertension where the SBP is usually more than 200 mmHg and/or the DBP is usually more than 120 mmHg. These patients are generally asymptomatic and do not have evidence of acute target organ damage. BP lowering may occur over hours to days in the absence of acute target organ damage or serious comorbid disease.

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 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 that may mimic hypertensive emergencies or urgencies such as panic attack or postictal hypertension.

The choice of an appropriate oral or parenteral antihypertensive medication for treatment of severe hypertension depends upon the type of hypertensive emergency, the presence of associated target organ damage, and the specific hemodynamic properties and side effects of the emergency or urgency. When possible, clinicians should opt for a gradual controlled reduction of BP and avoid antihypertensive agents or methods that have been associated with rapid or precipitous reductions in BP.

Catastrophic side effects including acute myocardial infarction, cortical blindness, stroke, and death have been reported with rapid or precipitous reduction in BP in patients presenting with hypertensive urgency or emergency. Treatment of hypertensive emergency needs to be tailored to each individual patient and presentation. Prompt and rapid reduction of BP under continuous surveillance is essential in patients who are symptomatic and have acute end-organ damage. Parenteral therapy, typically in a monitored bed in the intensive care unit, is recommended for the treatment of most hypertensive emergencies. Sodium nitroprusside is the "gold standard" for treating hypertensive emergencies, and the agent to which other parenteral agents are measured. Nitroprusside is metabolized to thiocyanate and cyanide, and may accumulate in patients receiving high doses, or prolonged infusions especially with CKD. Repeated intravenous injections ("mini bolus" of 10–20 mg) of the combined alpha- and beta-adrenergic receptor-blocking agent labetalol can produce a prompt but gradual reduction of arterial BP without the induction of a reflex tachycardia.

Hypertensive urgencies are usually treated with oral antihypertensive medications. Single oral agents or combinations of antihypertensive medications have been used to lower BP in this setting. Clinicians should avoid using short-acting oral or sublingual nifedipine in the treatment of hypertensive urgency and emergency, especially in those patients with known or suspected coronary artery disease.

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. Accurate BP measurement is well described by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) *(17)*, the World Health Organization–International Society of Hypertension (WHO/ISH) *(18)*, and the American Heart Association (AHA) *(19)*. 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 (1) resting for 5 min, (2) sitting with back supported and feet on the floor, (3) arm supported at heart level, (4) appropriate-size cuff applied, (5) use of the Korotkoff Phase I sound for SBP and Phase V for DBP, and (6) 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 auscultated 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

Home BP monitoring has become popular in clinical practice, and several automated devices for home BP measurement are now recommendable. 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 *(20)*. Home BP provides an opportunity for additional monitoring of BP levels and its variability.

2.7.3. Ambulatory BP

Ambulatory blood pressure (ABPM) provides automated measurements of brachial-artery 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. 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 *(21)*.

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 *(22*, *23)*.

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. Normal ranges for ABPM are average daytime ABPM of less than 135/85 mmHg and average nighttime ABPM less than 120/70 mmHg, but even lower values are advocated, particularly in high-risk groups such as diabetic patients (Table 3).

ABMP is accepted as being of benefit in patients with the conditions listed in Table 4. 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, and it shows BP behavior over a 24-h

Table 3
Recommended Levels of Normality for Ambulatory Blood Pressure Monitoring in Adults

	Blood pressure value (mmHg)		
	Optimal	*Normal*	*Abnormal*
Awake	<130/80	<135/85	>140/90
Asleep	<115/65	<120/70	>125/75

Table 4
Recommendations for the Use of Ambulatory Blood Pressure Monitoring in Clinical Practice

Indication	*JNC VII*	*WHO/ISH*
White-coat hypertension	Yes	Yes
Labile hypertension	Yes	Yes
Resistant hypertension	Yes	Yes
Hypotensive episodes	Yes	Yes
Postural hypotension	Yes	No

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, isolated systolic hypertension, and masked hypertension.

Self-monitoring of the BP at home and at work can be used to assess whether there is a large disparity between the office and out-of-office BPs before ambulatory monitoring is considered. It is likely that many patients whose self-monitored BP is apparently normal will have elevated ambulatory BP and would benefit from antihypertensive therapy. For those whose ambulatory BP is truly normal (<130/80 mmHg) despite an elevated office BP and in whom there is no evidence of other CV risk factors or target organ disease, avoidance of unnecessary drug therapy would be a clear benefit of the monitoring procedure.

2.8. EVALUATION OF HYPERTENSION

Following the confirmation of hypertension, a targeted history and physical examination and limited laboratory evaluation should be performed *(24, 25)*. The standard hypertensive workup 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 5. The medical history and physical examination are also the most important components of a pretreatment evaluation in differentiating between primary and secondary hypertension. The medical history should include detailed questioning which focuses on the following medical information.

Table 5
Cardiovascular 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:

1. Family history of premature CVD, diabetes, or dyslipidemia
2. Estimated duration of hypertension, current and previous hypertension stage, and drug therapy
3. Home BP measurements
4. Medical history, clinical signs, and symptoms of CV or renal disease
5. Medical history, clinical signs, and symptoms of comorbid disease, which may affect selection of drug therapy (asthma, chronic obstructive pulmonary disease [COPD])
6. Complete medication history including prescription, over-the-counter (OTC) medications, herbal remedies, and drug allergies
7. 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:

1. Vital signs, including body mass index (BMI)
2. Sitting and standing BP and heart rate
3. BP measurement in the contralateral arm
4. Examination of optic fundi, neck, heart, lungs, and abdomen
5. Auscultation of the neck and abdomen for bruits
6. Palpation of peripheral pulses, and extremity check for edema
7. Neurological examination

A limited laboratory evaluation is recommended at the time of initial diagnosis. This should include a complete blood cell count, serum 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 risk for developing coronary heart disease (CHD). Such risk assessments may be useful for estimating global CV risk and in modifying patient behavior. Given the higher than expected frequency of hyperlipidemia with hypertension, clinicians could elect to use the risk-scoring calculator developed by The National Cholesterol Education Program (NCEP). The NCEP now recommends using a modification of the Framingham risk prediction model to estimate CV risk and adjust therapy in patients with dyslipidemia *(26)*. The risk factors included in this Framingham calculation of 10-year risk are age, total cholesterol, high-density lipoprotein cholesterol, SBP, treatment for hypertension, and cigarette smoking. This modification of the Framingham point score does not account for all risk factors for CHD and should only be used in conjunction with NCEP guidelines. Separate NCEP Framingham risk calculators are available for men and women. Other risk factor calculators could be used for those patients who present without dyslipidemia.

2.9. TREATMENT

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 clinical goal is to lower BP to below 140/90 mmHg while controlling other CV risk factors. Further reductions in BP to a level less than 130/80 mmHg have been recommended in hypertensive patients with diabetes or renal disease. Reduction in BP to less than 130/80 mmHg can also be pursued with due regard in other populations, especially high-risk patients. Nondrug therapy should be employed in the management of all stages of hypertension and should also be implemented in individuals with prehypertension as a preventive strategy. New guidelines for diagnosis and treatment of hypertension—JNC VIII—are expected in 2011. The most recent ESH/ISH Guidelines for Diagnosis and Treatment of Hypertension were published in 2007 *(25)*.

The use of drug therapy is generally predicated on the stage of hypertension, the presence of high CV risk, comorbid conditions, and the documentation of target organ damage. For example, patients with prehypertension and specific comorbid conditions, such as diabetes mellitus or hypertensive nephropathy, may benefit from early drug therapy.

Lifestyle modification may prevent or delay the onset of sustained hypertension, lower BP, and reduce the number of BP medications necessary for control in patients with established hypertension. Comprehensive lifestyle modification has been well studied and includes the following interventions:

1. Weight reduction in those who are overweight or obese
2. Adoption of a Dietary Approaches to Stop Hypertension (DASH) diet—a low-fat diet rich in fruits, vegetables, and low-fat dairy products
3. Reduce sodium intake to 100 mmol/day (2.4 g sodium or 6 g sodium chloride)

4. Limit alcohol intake to ~1 oz/day (24 oz of beer per day, 8 oz of wine per day, or 2 oz of 100 proof whiskey per day)
5. Regular aerobic exercise
6. Stop smoking and modify other known CV risk factors

Adherence to one or several of these lifestyle modifications can result in a substantial fall in BP and aid in the management of hypertension. In general, weight loss and dietary changes have been observed to have the most dramatic effect on BP reduction *(27)*, a 1,600 mg sodium DASH eating plan has been shown to have effects on BP reduction similar to single-drug therapy *(28)*. Adoption of healthy lifestyles in both prehypertension and hypertension is critical for the prevention of future CVD.

Although the JNC VII guideline recommends the use of pharmacologic therapy in patients with BPs greater than or equal to 140/90 mmHg, many clinicians continue to initiate a 3- to 6-month trial of comprehensive lifestyle modification in highly motivated patients who have uncomplicated Stage I hypertension. Drug therapy should be considered if BP remains greater than or equal to 140/90 mmHg after 3–6 months or if the patient is noncompliant with nondrug therapy.

Multiple drug classes, with different mechanisms of action and different side effects, are available for the treatment of hypertension *(24*, *25)*. Table 6 summarizes the oral antihypertensive drugs. Several classes of antihypertensives, including diuretics, calcium antagonists, ACEIs, and angiotensin receptor antagonists, are suitable for the initiation and maintenance of antihypertensive therapy. Beta-blockers and alpha-blockers are less favored by many clinicians and guidelines as first-line therapy.

The selection of a specific medication for initial treatment of hypertension is complex and may depend on a variety of factors, including age and race, comorbid CV and non-CVD, and target organ damage. Potential drug–drug interactions with a patient's existing medical regimen may further limit therapeutic options. Repeated clinical observations have suggested that diuretics and CCBs may be more effective in standard doses in older patients and African Americans, while beta-blockers and ACEIs appear to be more effective in younger and Caucasian populations. Gender has not been found to be a reliable predictor for drug response. For the majority of patients without a compelling indication for another class of an antihypertensive medication, a low dose of a thiazide diuretic is frequently recommended as the first choice of therapy. Table 7 summarizes the preferential antihypertensive drugs in case of specific target organ damage or specific populations.

On average, no more than 50% of a hypertensive population will be controlled by a single antihypertensive medication. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in a population of older hypertensives with Stage I and II hypertension and high CV risk, BP was lowered to less than 140/90 mmHg in 66% of the population at 5 years. A total of 63% of the ALLHAT cohort were taking two or more medications at the end of the trial *(29)*.

Physicians have been notably reluctant to change or to add medications in those patients whose BPs are not at recommended goals. This phenomenon, which is commonly seen in the management of hypertension, is now referred to as "clinical inertia." Clinical inertia is defined as the failure of healthcare providers to initiate or intensify therapy when indicated *(30)*. Many physicians are still inclined to practice sequential monotherapy substituting individual agents in order to identify the most effective antihypertensive medication for a given patient and to limit the number of antihypertensive medications that a patient takes. The preferred strategy for the management of hypertension involves the use of multiple medications and utilizing the additive benefits of agents in combination. It is well recognized that the skillful use of two or more agents in combination can improve hypertension control rates to well above 80%.

In this chapter the different classes of antihypertensive drugs will be discussed in relation to subclasses with side effects and target population. Recently, a new class of antihypertensive drugs, the direct renin inhibitors (DRI), has been introduced and the first DRI, aliskiren, is now available for clinical use.

Table 6
Oral Antihypertensive Drugs

Drug	*Trade name*	*Usual dose range, total mg/day (frequency/day)*	*Selected side effects and comments*
Diuretics (partial list)			Short term: increases cholesterol and glucose levels; biochemical abnormalities; decreases potassium, sodium, and magnesium levels, increases uric acid and calcium levels; rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia
Chlorthalidone (G)	Hygroton	12.5–50 (1)	
Hydrochlorothiazide (G)	HydroDIURIL, Microzide, Esidrix	12.5–50 (1)	
Indapamide	Lozol	1.25–5 (1)	(Less or no hypercholesterolemia)
Metolazone	Mykrox	0.5–1.0 (1)	
	Zarxolyn	2.5–10 (1)	
Loop diuretics			
Bumetanide (G)	Bumex	0.5–4 (2–3)	(Short duration of action, no hypercalcemia)
Ethacrynic acid	Edecrin	25–100 (2–3)	(Only nonsulfonamide diuretic, ototoxicity)
Furosemide (G)	Lasix	40–240 (2–3)	(Short duration of action, no hypercalcemia)
Torsemide	Demadex	5–100 (1–2)	
Potassium-sparing agents			Hyperkalemia
Amiloride hydrochloride (G)	Midamor	5–10 (1)	
Spironolactone (G)	Aldactone	25–100 (1)	(Gynecomastia)
Triamterene (G)	Dyrenium	25–100 (1)	
Adrenergic inhibitors			
Peripheral agents			
Guanadrel sulfate	Hylorel	10–75 (2)	(Postural hypotension, diarrhea)
Fanethidine monosulfate	Ismelin	10–150 (1)	(Postural hypotension, diarrhea)
Reserpine (G)	Serpasil	0.05–0.25 (1)	(Nasal congestion, sedation, depression, activation of peptic ulcer)
Central alpha-agonist			Sedation, dry mouth, bradycardia, withdrawal hypertension
Clonidine hydrochloride (G)	Catapres	0.2–1.2 (2–3)	(More withdrawal)
Guanabenz acetate (G)	Wytensin	8–32 (2)	
Guanfacine hydrochloride (G)	Tenex	1–3 (1)	(Less withdrawal)
Methyldopa (G)	Aldomet	500–3,000 (2)	(Hepatic and “autoimmune” disorders)

(Continued)

Table 6
(Continued)

Drug	*Trade name*	*Usual dose range, total mg/day (frequency/day)*	*Selected side effects and comments*
Alpha-blockers			Can elevate HDL
Doxazosin mesylate	Cardura	1–16 (1)	
Prazosin hydrochloride (G)	Minipress	2–30 (2–3)	
Terazosin hydrochloride	Hytrin	1–20 (1)	
Beta-blockers			Bronchospasm, bradycardia, heart failure; may mask insulin-induced hypoglycemia; less serious: impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity), reduced HDL, impaired glyceric control
Acebutolol	Sectral	200–800 (1)	
Atenolol (G)	Tenormin	25–100 (1–2)	
Betaxolol hydrochloride	Kerlone	5–20 (1)	
Bisoprolol fumarate	Zebeta	2.5–10 (1)	
Carteolol hydrochloride	Cartrol	2.5–10 (1)	
Metoprolol tartrate (G)	Lopressor	50–300 (2)	
Metoprolol succinate	Toprol XL	50–300 (1)	
Nadolol	Corgard	40–320 (1)	
Penbutolol sulfate	Levatol	10–20 (1)	
Pindolol (G)	Visken	10–60 (1)	
Propranolol hydrochloride (G)	Inderal	40–480 (2)	
	Inderal LA	40–480 (1)	
Timolol maleate (G)	Blocadren	20–60 (2)	
Nebivolol	Bystolic	2.5–5–10 (1)	
Combined alpha and beta-blockers			Postural hypotension, bronchospasm
Carvedilol	Coreg	12.5–50 (2)	
Labetalol hydrochloride (G)	Normodyne, Trandate	200–1,200 (2)	
Direct vasodilators			
Hydralazine hydrochloride (G)	Apresoline	50–300 (2)	Headaches, fluid retention, tachycardia (Lupus syndrome)
Minoxidil	Loniten	5–100 (1)	(Hirsutism)

Calcium antagonists			
Nondihydropyridine			Conduction defects, worsening of systolic dysfunction, gingival hyperplasia
Diltiazem hydrochloride	Cardizem SR	120–360 (2)	(Nausea, headache)
	Cardizem CD, Dilacor XR, Tiazac	120–360 (1)	
Verapamil hydrochloride	Isoptin Sr, Calan SR	90–480 (2)	
	Verelan, Covera-HS	120–480 (1)	
Dihydropyridines			Edema of the ankle, flushing, headache, gingival hypertrophy
Amlodipine besylate	Norvasc	2.5–10 (1)	
Felodipine	Plendil	2.5–10 (1)	
Isradipine	DynaCirc	5–20 (2)	
	DynaCirc CR	5–20 (1)	
Nicardipine hydrochloride	Cardene SR	60–90 (2)	
Nifedipine	Procardia XL, Adalat CC	30–120 (1)	
Nisoldipine	Sular	20–60 (1)	
Angiotensin-converting enzyme inhibitors			Common: cough; rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia
Benazepril hydrochloride	Lotensin	5–40 (1–2)	
Captopril (G)	Capoten	25–150 (2–3)	
Enalapril maleate	Vasotec	5–40 (1–2)	
Fosinopril sodium	Monopril	10–40 (1–2)	
Lisinopril	Prinivil, Zestril	5–40 (1)	
Moexipril hydrochloride	Univasc	7.5–15 (2)	
Quinapril hydrochloride	Accupril	5–80 (1–2)	
Ramipril	Altace	1.25–20 (1–2)	
Trandolapril	Mavik	1–4 (1)	
Angiotensin II receptor blockers			Angioedema (very rare); hyperkalemia
Losartan potassium	Cozaar	25–100 (1–2)	
Valsartan	Diovan	80–320 (1)	

(Continued)

Table 6
(Continued)

Drug	*Trade name*	*Usual dose range, total mg/day (frequency/day)*	*Selected side effects and comments*
Irbesartan	Avapro	150–300 (1)	
Telmisartan	Micardis	20–80 (1)	
Olmesartan	Benicar	20–40 (1)	
Candesartan	Atacand	8–32 (1–2)	
Direct renin inhibitor	Tekturna	150–300 (1)	Angioedema (very rare); hyperkalemia
Combination formulations			
Enalapril maleate/felodipine	Lexxel	5/5 (1)	Angioedema (very rare); hyperkalemia; edema from the CCB component
Trandolapril/verapamil	Tarka	2/180, 1–4/240 (1)	
Amlodipine/benazepril hydrochloride	Lotrel	2.5–10/10–20	
Amlodipine/valsartan	Exforge	5–160/10–160/5–320/ 10–320	

Table 7
Antihypertensive Therapy in Function of Target Organ Damage

Heart
Left ventricular hypertrophy: ACE-I, ARB, CA
Previous myocardial infarction: BB, ACE-I, ARB
Coronary artery disease—angina pectoris: BB, CCB
Heart failure: diuretics, BB, ACE-I, ARB, antialdosterone antagonists
Left ventricular dysfunction: ACE-I
Atrial fibrillation:
Permanent: BB, nondihydropyridine CCB
Recurrent: ACE-I, ARB
Tachyarrhythmias: BB
Noncoronary atherosclerosis
Poststroke: any antihypertensive drug
Peripheral artery disease: CCB
Kidney
Microalbuminuria/proteinuria: ACE-I, ARB
Renal dysfunction: ACE-I, ARB
End-stage renal disease: ACE-I, ARB
Special groups
Isolated hypertension (elderly): diuretics, CA
Metabolic syndrome: ACE-I, ARB, CCB
Diabetes mellitus: ACE-I, ARB
Pregnancy: methyldopa, CCB, BB
Glaucoma: BB
ACE-I-induced cough: ARB

ACE-I = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, BB = beta-blockers, CCB = calcium channel blockers, CA = calcium antagonists.

2.9.1. Diuretics

It has been well documented that diuretics are effective antihypertensive drugs. Hydrochlorothiazide at a dose of 12.5 mg or 25 mg/day is the most frequently used diuretic. Chlorthalidone is also very effective. Diuretics cause salt and water depletion. The most important side effects are hypokalemia, hyperuricemia, impotence, and risk for diabetes in the long term. Thiazides are less effective in conditions of renal impairment (eGFR < 30 mL/min). In these cases furosemide can be used as an alternative therapy. Thiazides can be combined with a potassium-sparing diuretic like triamterene or spironolactone. Aldosterone antagonists, spironolactone and eplerenone, are potassium-sparing diuretics but should be considered in a category of a RAAS blocker, because of their ancillary cardiovascular protective effects beyond their diuretic effect. Electrolytes need to be monitored for hyperkalemia. Gynecomastia is a side effect, especially with spironolactone use. In patients on diuretic therapy, renal function should be monitored.

2.9.2. Beta-blockers

Beta-blockers can be categorized into nonselective (propranolol), cardio-selective (metoprolol, atenolol), with intrinsic sympathomimetic activity (pindolol), or with an alpha-blocking effect (labetolol, carvedilol). Most of the beta-blockers are metabolized by the liver, while atenolol is cleared by the kidney. Therefore, caution should be taken when atenolol is used in cases of renal impairment and dosing needs to be adapted. Beta-blockers are indicated in hypertensive patients

with angina, postmyocardial infarction, and postrevascularization either with balloon angioplasty or coronary bypass grafting. Beta-blockers should be avoided in patients with asthma, chronic obstructive pulmonary disease, or heart block.

2.9.3. ACE-inhibitors

ACE-inhibitors block the RAAS by inhibiting the angiotensin-converting enzyme, leading to less conversion of angiotensin I to angiotensin II. ACE-inhibitors are indicated in hypertensive patients with diabetes mellitus, impaired renal function, microalbuminuria or proteinuria, postmyocardial infarction, coronary artery disease, heart failure, and poststroke. Angioedema is the most severe side effect but very rare. The most frequent side effect is cough. Hyperkalemia is sometimes found if renal function is not monitored. ACE-inhibitors are contraindicated during pregnancy.

2.9.4. Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARB) block the RAAS by blocking the angiotensin II type 1 receptor. ARBs are indicated in hypertensive patients with diabetes, impaired renal function, microalbuminuria or proteinuria, postmyocardial infarction, and heart failure. Side effects are rare. Hyperkalemia is sometimes found if renal function is not monitored. ARBS are contraindicated during pregnancy. ARBs have a role in patients who are intolerant to ACE-inhibitors.

2.9.5. Direct Renin Inhibitors

The RAAS blockers (ACE-I and ARB) further activate the RAAS, leading to an increase of plasma renin activity and plasma renin concentration. After decades of research, an oral renin inhibitor, aliskiren, has been developed *(31)*. Aliskiren is the first orally active direct renin inhibitor and is an effective and well-tolerated antihypertensive agent when used in monotherapy or in combination with other antihypertensive agents in patients with mild to moderate hypertension. In contrast with ACE-I and ARBs, aliskiren reduces plasma renin activity. A number of clinical trials with aliskiren are ongoing or completed and provide us with objective evidence regarding the clinical importance of direct renin inhibition in the treatment of cardiovascular disease.

2.9.6. Calcium Channel Blockers

Calcium channel blockers (CCB) are categorized in two groups: dihydropyridines and nondihydropyridines. The nondihydropyridines are verapamil and diltiazem and their slow-releasing preparations. The dihydropyridines are nifedipine (short- and long-acting), nisoldipine, nicardipine, amlodipine, felodipine, and isradipine. They are effective in lowering blood pressure. The most frequent side effects of the dihydropyridines are flushing and ankle edema. Ankle edema can be avoided by administrating the long-acting calcium antagonist at bedtime. The nondihydropyridines have an effect on the sinus node and AV conduction. So, attention needs to be paid in cases of low heart rate or heart block. CCBs also have a negative inotropic effect and, therefore, one needs to be cautious about their use in the presence of heart failure.

2.9.7. Alpha-1 Blockers

Alpha-1 blockers (doxazosin, terazosin) are used in case of prostate hypertrophy. One of the side effects is orthostatic hypotension. In the ALLHAT trial doxazosin was stopped because of an increased number of cardiovascular events.

2.9.8. Central Alpha-2 Agonists and Other Centrally Acting Drugs

The most frequently used in this category are clonidine and methyldopa. Methyldopa is still the most preferred antihypertensive agent during pregnancy because of its extensive record of safety over years. Clonidine is used less these days because of its side effects such as dry mouth, sleepiness, and, last but not the least, its risk for rebound phenomena when stopping it abruptly.

2.9.9. Direct Vasodilators

In cases of severe hypertension, direct vasodilators such as hydralazine and minoxidil can be used. They cause reflex tachycardia and, by stimulating RAAS, they will lead to sodium and fluid retention. Therefore, when hydralazine or minoxidil is used, diuretics should simultaneously be used. Hydralazine and nitrates have been very effective in heart failure in cases of hypertensive cardiomyopathy.

2.10. GUIDELINES FOR TREATMENT OF HYPERTENSION

2.10.1. Joint National Committee VII Guidelines

The therapeutic recommendations in JNC VII are in great part predicated on the findings of ALLHAT *(29)*. In the meantime, several landmark trials (discussed in the next section) with antihypertensive drugs have not been incorporated into these recommendations. The new highlights are:

1. In those older than age 50, SBP greater than or equal to 140 mmHg is a more important CVD risk factor than DBP.
2. CVD risk doubles for each increment of 20/10 mmHg beginning at 115/75 mmHg.
3. Even those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.
4. Individuals with prehypertension now defined as SBP 120–139 mmHg or DBP 80–89 mmHg require health-promoting lifestyle modifications to prevent the progressive rise in BP and CVD.
5. In uncomplicated primary hypertension, thiazide diuretics should be used in drug treatment for most, either alone or combined with drugs from other classes. With the evidence we have now, it seems that ACE-I together with dihydropyridines would be more effective in reducing cardiovascular morbidity and mortality.
6. High-risk conditions that are generally defined by concomitant CVD are now recognized as compelling indications for the use of other antihypertensive drug classes (ACEIs, ARBs, beta-blockers, and CCBs).
7. Two or more antihypertensive medications will be required to achieve goal BP (<140/90 mmHg or <130/80 mmHg) for many patients with primary hypertension and those with diabetes and CKD.
8. In patients whose BP is more than 20 mmHg above the SBP goal or more than 10 mmHg above the DBP goal, initiation of therapy using two antihypertensive agents, one of which usually will be a thiazide diuretic, should be considered.
9. Hypertension will be controlled only if patients are motivated to stay on their treatment.

These themes were in part designed to correct persistent and prevalent misperceptions surrounding the treatment of hypertension, including the following: that most cases of hypertension can be controlled with one antihypertensive medication, that DBP is a better indicator than SBP for advancing or intensifying antihypertensive therapy, and that the age-related increase in SBP is normal. A stated goal of JNC VII was to present clinicians with a streamlined, clear, and concise guideline for the classification and management of hypertension. As a result, the classification of hypertension, the integration of CV risk into the treatment paradigm, and treatment recommendations were simplified. Figure 1 shows a simplified algorithm.

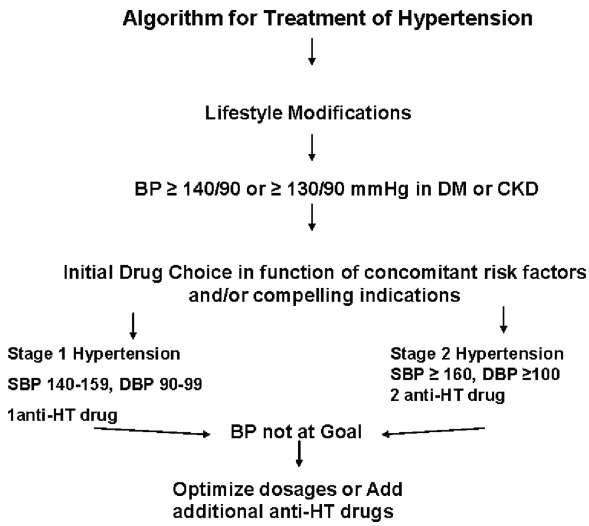

Fig. 1. Treatment of arterial hypertension (simplified from JNC VII). DM = diabetes, CKD = chronic kidney disease, anti-HT = antihypertensive.

2.11. RECENT LANDMARK HYPERTENSION TRIALS: IMPLICATIONS FOR EVIDENCE-BASED MEDICINE

A new series of trials has been completed, and several other trials started in efforts to further elucidate the effects of ACEIs, ARBs, CCBs, and other BP-lowering drugs on mortality and major CV morbidity in several populations of patients, including those with hypertension, diabetes mellitus, CHD, or renal disease.

The overview of placebo-controlled trials of ACEIs revealed 30% reductions in stroke, 20% in CHD, and 21% in major CV events. The overview of placebo-controlled trials of calcium antagonists showed 39% reductions in stroke and 28% in major CV events. In the overview of trials comparing BP-lowering strategies of different intensity, there were reduced risks of stroke (20%), CHD (19%), and major CV events (15%) with more intensive therapy *(32)*. Several landmark trials in hypertension treatment have been published, providing more evidence-based medicine data regarding optimal treatment of hypertension to reduce CV morbidity and mortality.

2.11.1. Intervention as a Goal in Hypertension Treatment

The Intervention as a Goal in Hypertension Treatment (INSIGHT) study was a prospective, randomized, double-blind trial in 6,321 patients, aged 55–80 years with hypertension (BP greater than or equal to 150/95 mmHg, or greater than or equal to 160 mmHg systolic) *(33)*. Patients had at least one additional CV risk factor. Patients were randomly assigned to nifedipine 30 mg in a long-acting gastrointestinal transport system (GITS) formulation, or co-amilozide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg). Dose titration was by dose doubling, and addition of atenolol 25–50 mg or enalapril 5–10 mg. The primary outcome was CV death, myocardial infarction, heart failure, or stroke. Analysis was done by intention to treat. Primary outcomes occurred in 200 (6.3%) of the patients in the nifedipine group and in 182 (5.8%) in the co-amilozide group (18.2 versus 16.5 events per 1,000 patient-years; relative risk 1.10 [95% CI 0.91–1.34], $p = 0.35$). Overall mean BP dropped from 173/99 to 138/82 mmHg. There was an 8% excess of withdrawals from the nifedipine group because of peripheral edema, but serious adverse events were more frequent in the co-amilozide group ($p = 0.02$). Deaths were mainly nonvascular (nifedipine 176 versus co-amilozide 172; $p = 0.81$). Nifedipine

once daily and co-amilozide were equally effective in preventing overall CV or cerebrovascular complications.

2.11.2. European Lacidipine Study on Atherosclerosis

The European Lacidipine Study on Atherosclerosis (ELSA) study was a randomized, double-blind trial in 2,334 patients with hypertension that compared the effects of a 4-year treatment based on either lacidipine or atenolol on an index of carotid atherosclerosis, the mean of the maximum intima-media thickness (IMT) in the far walls of the common carotids and bifurcations (CBMmax) *(34)*. The yearly IMT progression rate was 0.0145 mm/year in the atenolol-treated and 0.0087 mm/year in the lacidipine-treated patients (completers, 40% reduction; $p = 0.0073$). Patients with plaque progression were significantly less common, and patients with plaque regression were significantly more common in the lacidipine group. Clinic BP reductions were identical in both treatments, but 24-h ambulatory SBP/DBP changes were greater with atenolol (10/9 mmHg) than with lacidipine (7/5 mmHg). No significant difference between treatments was found in any CV events, although the relative risk for stroke, major CV events, and mortality showed a trend favoring lacidipine. The greater efficacy of lacidipine on carotid IMT progression and number of plaques per patient, despite a smaller ambulatory BP reduction, indicates an antiatherosclerotic action of lacidipine independent of its antihypertensive action.

2.11.3. Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis

The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study was a double-blind, randomized, multicenter 24-month trial comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented coronary artery disease (CAD > 20% stenosis by coronary angiography) and DBP less than 100 mmHg *(35)*. A substudy of 274 patients measured atherosclerotic progression by intravascular ultrasound (IVUS). Patients were randomized to receive amlodipine 10 mg, enalapril 20 mg, or placebo. IVUS was performed at baseline and study completion. The primary efficacy parameter was the incidence of CV events for amlodipine versus placebo. Other outcomes included comparisons of amlodipine versus enalapril and enalapril versus placebo. CV events included CV death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS substudy normalized endpoint was change in atheroma volume. Baseline BP averaged 129/78 mmHg for all patients; it increased by 0.7/0.6 mmHg in the placebo group and decreased by 4.8/2.5 mmHg and 4.9/2.4 mmHg in the amlodipine and enalapril groups, respectively ($p < 0.001$ for both versus placebo). CV events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54–0.88, $p = 0.003$), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67–1.07, $p = 0.16$). Primary endpoint comparison for enalapril versus amlodipine was not significant (HR, 0.81; 95% CI, 0.63–1.04, $p = 0.10$). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group versus placebo ($p = 0.12$), with significantly less progression in the subgroup with SBPs greater than the mean ($p = 0.02$). Compared with baseline, IVUS showed progression in the placebo group ($p < 0.001$), a trend toward progression in the enalapril group ($p = 0.08$), and no progression in the amlodipine group ($p = 0.31$). For the amlodipine group, correlation between BP reduction and progression was $r = 0.19$, $p = 0.07$. Administration of amlodipine to patients with CAD and normal BP resulted in a reduction of adverse CV events. Directionally similar, but smaller and nonsignificant treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing atherosclerosis progression.

2.11.4. Controlled Onset Verapamil Investigation of CV Endpoints

The Controlled Onset Verapamil Investigation of CV Endpoints (CONVINCE) trial was a randomized trial, double-blind, actively controlled multicenter, international clinical trial designed to test the hypothesis of equivalence of two antihypertensive drug regimens, beginning either with controlled-onset, extended-release verapamil or the investigator's preselected choice of either atenolol or hydrochlorothiazide in reducing CV events *(36)*. A total number of 16,602 hypertensive patients were enrolled with one or more additional CV risk factors. The primary objective was to compare the two regimens in preventing acute myocardial infarction, stroke, or CVD-related death. Major secondary outcomes included (1) an expanded CVD endpoint (hospitalization for angina, cardiac revascularization or transplant, heart failure, transient ischemic attacks or carotid endarterectomy, accelerated or malignant hypertension, or renal failure in addition to primary outcome); (2) all cause mortality; (3) cancer; (4) hospitalization for bleeding (excluding hemorrhagic stroke); and (5) incidence of primary endpoints occurring between 6:00 a.m. and noon. The overall results did not differ significantly by treatment group, and the prespecified equivalence criteria were not met. In addition, treatment differences for the major endpoints were consistent for four geographical regions defined a priori—United States, Canada, Western Europe, and "other countries."

2.12. VALSARTAN ANTIHYPERTENSIVE LONG-TERM USE EVALUATION (VALUE) TRIAL

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to test the hypothesis that for the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high CV risk *(37*, *38)*. A total number of 15,245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events participated in a randomized, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine. Duration of treatment was event driven and the trial lasted until at least 1,450 patients had reached a primary endpoint, defined as a composite of cardiac mortality and morbidity. Patients from 31 countries were followed up for a mean of 4.2 years. BP was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (BP 4.0/2.1 mmHg lower in amlodipine than valsartan group after 1 month; 1.5/1.3 mmHg after 1 year; $p < 0.001$ between groups). The primary composite endpoint occurred in 810 patients in the valsartan group (10.6%, 25.5 per 1,000 patient-years) and 789 in the amlodipine group (10.4%, 24.7 per 1,000 patient-years; HR 1.04, 95% CI 0.94–1.15, $p = 0.49$). The main outcome of cardiac disease did not differ between the treatment groups. Unequal reductions in BP might account for differences between the groups in cause-specific outcomes. The findings emphasized the importance of prompt BP control in hypertensive patients at high CV risk. The VALUE trial was designed to test whether, for the same achieved BPs, regimens based on valsartan or amlodipine would have differing effects on CV endpoints in high-risk hypertension. But inequalities in BP favoring amlodipine throughout the multiyear trial limited the comparison of outcomes.

2.13. ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT)

The apparent shortfall in prevention of CHD noted in early hypertension trials has been attributed to potential metabolic disadvantages of the diuretic and beta-blocker therapy. For a given reduction in BP, some suggested that newer agents would confer advantages over diuretics and beta-blockers. The aim of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was to compare the effect on nonfatal myocardial infarction and fatal CHD of combinations of atenolol with a thiazide versus amlodipine with perindopril. The ASCOT was a multicenter, prospective, randomized controlled

trial in 19,257 patients with hypertension who were aged 40–79 years and had at least three other CV risk factors *(39)*. Patients were assigned either amlodipine 5–10 mg, adding perindopril 4–8 mg as required (amlodipine-based regimen; $n = 9{,}639$), or atenolol 50–100 mg, adding bendroflumethiazide 1.25–2.5 mg and potassium as required (atenolol-based regimen; $n = 9{,}618$). The primary endpoint was nonfatal myocardial infarction (including silent myocardial infarction) and fatal CHD. Analysis was by intention to treat. The study was stopped prematurely by the DSMI after 5.5 years' median follow-up and accumulated in total 106,153 patient-years of observation. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 versus 474; unadjusted HR 0.90, 95% CI 0.79–1.02, $p = 0.1052$), fatal and nonfatal stroke (327 versus 422; 0.77, 0.66–0.89, $p = 0.0003$), total CV events and procedures (1,362 versus 1,602; 0.84, 0.78–0.90, $p < 0.0001$), and all cause mortality (738 versus 820; 0.89, 0.81–0.99, $p = 0.025$). The incidence of developing diabetes was less on the amlodipine-based regimen (567 versus 799; 0.70, 0.63–0.78, $p < 0.0001$). The amlodipine-based regimen prevented more major CV events and induced less diabetes than the atenolol-based regimen.

2.13.1. Conduit Artery Function Evaluation (CAFE) Trial

Different BP-lowering drugs could have different effects on central aortic pressures and, thus, CV outcome despite similar effects on brachial BP. The Conduit Artery Function Evaluation (CAFE) study, a substudy of ASCOT, examined the impact of two different BP-lowering regimens (atenolol thiazide-based versus amlodipine–perindopril-based therapy) on derived central aortic pressures and hemodynamics. The CAFE study recruited 2,199 patients in five ASCOT centers *(40)*. Radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressures and hemodynamic indexes on repeated visits for up to 4 years. Most patients received combination therapy throughout the study. Despite similar brachial SBPs between treatment groups (Δ 0.7 mmHg; 95% CI, 0.4–1.7; $p = 0.2$), there were substantial reductions in central aortic pressures with the amlodipine regimen (central aortic SBP, Δ 4.3 mmHg; 95% CI, 3.3–5.4; $p < 0.0001$; central aortic PP, Δ 3.0 mmHg; 95% CI, 2.1–3.9; $p < 0.0001$). Cox proportional hazards modeling showed that central PP was significantly associated with a post-hoc-defined composite outcome of total CV events/procedures and development of renal impairment in the CAFE cohort (unadjusted, $p < 0.0001$; adjusted for baseline variables, $p < 0.05$). BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP. Moreover, central aortic PP may be a determinant of clinical outcomes, and differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the two BP treatment arms in ASCOT.

2.14. TRIAL OF PREVENTION OF HYPERTENSION (TROPHY)

Prehypertension is considered a precursor of Stage I hypertension and a predictor of excessive CV risk. The Trial of Preventing Hypertension (TROPHY) studied whether pharmacologic treatment of prehypertension prevents or postpones Stage I hypertension *(41)*. Participants with repeated measurements of systolic pressure of 130–139 mmHg and diastolic pressure of 89 mmHg or lower, or systolic pressure of 139 mmHg or lower and diastolic pressure of 85–89 mmHg, were randomly assigned to receive 2 years of candesartan or placebo, followed by 2 years of placebo for all. When a participant reached the study endpoint of Stage I hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce BP throughout the trial. A total of 409 participants were randomly assigned to candesartan and 400 to placebo. Data on 772 participants (391 in the candesartan group and 381 in the placebo group; mean age, 48.5 years; 59.6% men) were available for analysis. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 of those in the candesartan group (relative risk reduction, 66.3%; $p < 0.001$). After 4 years, hypertension had developed in 240 participants in the

placebo group and 208 of those in the candesartan group (relative risk reduction, 15.6%; $p < 0.007$). Over a period of 4 years, Stage I hypertension developed in nearly two thirds of patients with untreated prehypertension (the placebo group). Treatment of prehypertension with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period. Thus, treatment of prehypertension appears to be feasible. However, we need to learn who should be treated, for how many years, and with which drug and at what dose. For now, a healthy lifestyle is the foundation for all therapies in persons with prehypertension. This is still true even after the lessons of the TROPHY study.

2.15. ACCOMPLISH TRIAL

The optimal combination drug therapy for hypertension is not established, although current US guidelines recommend inclusion of a diuretic. The ACCOMPLISH trial hypothesized that treatment with the combination of an angiotensin-converting enzyme (ACE) inhibitor and a dihydropyridine calcium channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE-inhibitor plus a thiazide diuretic *(42)*. In a randomized, double-blind trial, we assigned 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The trial was terminated early after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. Mean blood pressures after dose adjustment were 131.6/73.3 mmHg in the benazepril–amlodipine group and 132.5/74.4 mmHg in the benazepril–hydrochlorothiazide group. There were 552 primary-outcome events in the benazepril–amlodipine group (9.6%) and 679 in the benazepril–hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril–amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72–0.90; $p < 0.001$). For the secondary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke the hazard ratio was 0.79 (95% CI, 0.67–0.92; $p = 0.002$). Rates of adverse events were consistent with those observed from clinical experience with the study drugs. In conclusion, the benazepril–amlodipine combination was superior to the benazepril–hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.

2.16. HYVET

Whether the treatment of patients with hypertension who are 80 years of age or older is beneficial is unclear. It has been suggested that antihypertensive therapy may reduce the risk of stroke, despite possibly increasing the risk of death. In the HYVET trial 3,845 patients who were 80 years of age or older and had a sustained systolic blood pressure of 160 mmHg or more were randomly assigned to either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo *(43)*. The angiotensin-converting enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mmHg. The primary endpoint was fatal or nonfatal stroke. The active-treatment group (1,933 patients) and the placebo group (1,912 patients) were well matched (mean age, 83.6 years; mean blood pressure while sitting, 173.0/90.8 mmHg); 11.8% had a history of cardiovascular disease. Median follow-up was 1.8 years. At 2 years, the mean blood pressure while sitting was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval [CI], 1–51; $p = 0.06$), a 39% reduction in the rate of

death from stroke (95% CI, 1–62; $p = 0.05$), a 21% reduction in the rate of death from any cause (95% CI, 4–35; $p = 0.02$), a 23% reduction in the rate of death from cardiovascular causes (95% CI, 1–40; $p = 0.06$), and a 64% reduction in the rate of heart failure (95% CI, 42–78; $p < 0.001$). Fewer serious adverse events were reported in the active-treatment group (358 versus 448 in the placebo group; $p = 0.001$). The results of the HYVET trial provide evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial.

2.17. ON TARGET

In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. The ON TARGET trial was a comparison between the ACE-inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes *(44)*. After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8,576 assigned to receive 10 mg of ramipril per day, 8,542 assigned to receive 80 mg of telmisartan per day, and 8,502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mmHg greater reduction) and the combination-therapy group (a 2.4/1.4 mmHg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1,412 patients in the ramipril group (16.5%), as compared with 1,423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94–1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% versus 4.2%, $p < 0.001$) and angioedema (0.1% versus 0.3%, $p = 0.01$) and a higher rate of hypotensive symptoms (2.6% versus 1.7%, $p < 0.001$); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1,386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92–1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% versus 1.7%, $p < 0.001$), syncope (0.3% versus 0.2%, $p = 0.03$), and renal dysfunction (13.5% versus 10.2%, $p < 0.001$). The results showed that telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit. This study is very helpful in the establishment of new hypertension guidelines.

In conclusion, diagnosis and treatment of arterial hypertension remains a challenge. Since the JNC VII guidelines were published, there has been a large number of new landmark trials that provide significant new insights into how hypertension can be managed in the most efficacious manner possible.

2.18. CASE STUDIES

2.18.1. Case Study 1—Hypertensive Emergency

A 52-year-old white women presents to the emergency room with complaints of severe headache with a severity of 9/10, blurred vision, and shortness of breath. She smokes about a half pack cigarettes/day. She has a family history of arterial hypertension and stroke. She is 3 year post-menopausal. Her blood pressure was measured the past years sporadically and varied between 135 and 160 mmHg systolic and 85 and 95 mmHg diastolic. However, the patient was reluctant to take antihypertensive medication beyond salt restriction and dietary advice, which was not followed very well.

Physical examination in the emergency room revealed:

Blood pressure right arm: 226/118 mmHg; blood pressure left arm: 230/120 mmHg
Pulse: 66 bpm
BMI: 29.2 kg/m^2
Physical exam: alert and awake
Head and neck: no carotid bruits, no jugular vein distension
Heart: prominent S2, regular rhythm, no bruit
Lung: few basilar crackles
Abdomen: no bruits over renal arteries
Extremities: decreased pulses at both tibial arteries 3+/4
Neurological exam: normal
Optic fundi: retinal bleedings

2.18.1.1. Laboratory Data (Initial Tests)

Sodium 138 mEq/L (136–145)
Potassium 4.1 mEq/L (3.5–5.0)
Chloride 110 mEq/L (98–110)
Calcium 9.2 mEq/L (8.8–10.0)
Blood urea nitrogen 23.0 mg/dL (8.0–22.0)
Creatinine 1.3 mg/dL (0.5–1.2)
eGFR 46 mL/min/1.73 m^2
Glucose 118 mg/dL (70–110)

2.18.1.2. Issues and Discussion Points

2.18.1.2.1. What Is the Difference Between a Hypertensive Emergency and Urgency? Hypertensive emergencies require prompt recognition and thoughtful management in order to reduce the morbidity and mortality associated with severe hypertension. BP reduction typically is begun within minutes to hours of diagnosis and is frequently required to prevent worsening of an underlying clinical condition.

The term "hypertensive urgency" refers to a clinical presentation of severe hypertension where the SBP is usually more than 200 mmHg and/or the DBP is usually more than 120 mmHg. These patients are generally asymptomatic and do not have evidence of acute target organ damage. BP lowering may occur over hours to days in the absence of acute target organ damage or serious comorbid disease.

2.18.1.2.2. How Would You Manage This Hypertensive Emergency Case? Treatment of hypertensive emergency needs to be tailored to each individual patient and presentation. Prompt and rapid reduction of BP under continuous surveillance is essential in patients who are symptomatic and have acute end-organ damage. Parenteral therapy, typically in a monitored bed in the intensive care unit, is recommended for the treatment of most hypertensive emergencies. Sodium nitroprusside is the "gold standard" for treating hypertensive emergencies and the agent to which other parenteral agents are measured.

Repeated intravenous injections ("mini bolus" of 10–20 mg) of the combined alpha- and beta-adrenergic receptor-blocking agent labetalol can produce a prompt but gradual reduction of arterial BP without the induction of a reflex tachycardia. Repeated intravenous injections ("mini bolus" of 10–20 mg) of the combined alpha- and beta-adrenergic receptor-blocking agent labetalol can produce a prompt but gradual reduction of arterial BP without the induction of a reflex tachycardia. This patient received a sodium nitroprusside infusion and also a bolus of furosemide because of the development of acute heart failure.

2.18.1.2.3. Which Tests Do You Perform in Cases of Hypertensive Emergency/Urgency? The patient needs an extensive workup with a blood exam (CBC, basic metabolic panel consisting of electrolytes, renal parameters, glucose, lipid profile, and thyroid function). A urine evaluation for microalbuminuria or proteinuria is mandatory as well for cell casts. An ECG is done to rule out rhythm abnormalities, myocardial ischemia, and left ventricular hypertrophy. An echocardiogram provides information about myocardial and valvular function. Depending upon clinical symptoms and physical examination findings, ancillary tests will be performed to rule secondary causes of secondary hypertension.

2.18.1.2.4. Which Chronic Antihypertensive Therapy? In addition to the nitroprusside infusion and intravenous furosemide during the first 24 h, a beta-blocker (metoprolol) was started together with the calcium antagonist amlodipine at bedtime (evening dosing of this medication reduces lower extremity edema compared to giving it in the morning). An ACE-inhibitor was also started in a low dose beyond oral furosemide. A renal panel and electrolytes were checked during follow-up. The patient was provided extensive information to quit smoking. Because of the presence of hypercholesterolemia and hypertension, statin therapy was started. The patient was also started on aspirin therapy as well because during the workup, the patient was diagnosed with peripheral arterial disease.

2.18.2. Case Study 2—Chronic Poorly Controlled Hypertension with Patient Referred to a Hypertension Specialist

A 61-year-old African-American male with arterial hypertension for 25 years is referred to a hypertension specialist clinic because of resistant hypertension. He feels tired and has COPD. He quit smoking about 1 year ago. He has received several antihypertensive medications to lower his blood pressure including hydrochlorothiazide, chlorthalidone, nadolol, atenolol, metoprolol, alpha-methyldopa, clonidine, nifedipine, felodipine, captopril, and hydralazine in different combinations and at several doses. However, blood pressure never reached goal, especially systolic blood pressure, which varied between 140–160 mmHg despite different antihypertensive regimen and between 85 and 95 mmHg for the diastolic blood pressure.

Family history: mother died from a stroke at age 63 years and father died from sudden cardiac death at age 59 years. Multiple siblings have hypertension.

Physical examination:

Blood pressure right arm: 158/90 mmHg; Blood pressure left arm: 154/92 mmHg
Pulse: 74 bpm
BMI: 28.7 kg/m^2
Head and neck: bruit at right common carotid artery, no jugular vein distension
Heart: systolic murmur 1/6 left parasternal border
Lung: decreased breath sounds
Abdomen: no bruits over renal arteries
Extremities: decreased pulses at both dorsal and tibial posterior arteries
Neurological exam: normal

2.18.2.1. Laboratory Tests

Sodium 137 mEq/L (136–145)
Potassium 3.7 mEq/L (3.5–5.0)
Chloride 107 mEq/L (98–110)
Calcium 9.2 mEq/L (8.8–10.0)
Blood urea nitrogen 25.0 mg/dL (8.0–22.0)
Creatinine 1.32 mg/dL (0.5–1.2)

eGFR 71 mL/min/1.73 m^2
Glucose 114 mg/dL (70–110)
Total cholesterol 248 mg/dL (<200)
LDL-cholesterol 147 mg/dL (<130)
HDL-cholesterol 39 mg/dL (>40)
Triglycerides 156 mg/dL (<150)
Albuminuria/creatinine ratio (μg/mg) 32

2.18.2.2. Issues and Discussion Points

2.18.2.2.1. What Is Resistant Hypertension? Resistant or "hard-to-treat" hypertension is generally defined as the failure to achieve a therapeutic target of less than 140/90 mmHg in most hypertensive patients, or less than 130/80 mmHg in diabetics or patients with chronic kidney disease, on a well-designed three-drug antihypertensive medical regimen combined with intensive lifestyle modification diuretic therapy. In most cases, resistant hypertension is now defined on the basis of a persistently high systolic blood pressure level.

2.18.2.2.2. Which Antihypertensive Treatment Plan Do You Establish? The antihypertensive regimen for this patient was constructed on the following basis: African-American hypertensive patients react very well to diuretics and calcium antagonists. Therefore, we recommended hydrochlorothiazide 25 mg/day and amlodipine 10 mg at bedtime. Because of his extensive COPD and prediabetes he was not given a beta-blocker. The patient was continued on lisinopril 20 mg/day. Resistant hypertensive patients respond very well to aldosterone antagonists. This patient was given spironolactone 12.5 mg/day and was followed-up with electrolytes and renal function indices within 1 week. Arterial blood pressure after 1 week was 148/82 mmHg. Because it is known that African Americans have endothelial dysfunction and often have a decreased synthesis of nitric oxide, we added isosorbide dinitrate 30 mg/day in the morning. It is known that nitrates effectively lower central aortic blood pressure more than peripheral pressure and have a beneficial effect on systolic blood pressure. As a consequence blood pressure decreased to 135/78 mmHg. The patient also received statin therapy and aspirin (81 mg/day).

2.18.2.2.3. Should We Go for a Tailored Antihypertensive Therapy? There is a change in the concept that arterial hypertension is an expression of an already-existing vascular disease in which endothelial dysfunction is often the beginning detrimental factor. When arterial hypertension is diagnosed, there are often concomitant risk factors and target organ damage such as microalbuminuria, left ventricular hypertrophy, and carotid artery disease. Many hypertensive patients have type 2 diabetes or the metabolic syndrome. Therefore, the choice of antihypertensive therapy needs to be directed not only by the blood pressure lowering effect, but also by its capacity to reduce insulin resistance or to provide renal protection.

2.18.2.2.4. Should We Titrate Antihypertensive Therapy to a Maximum Dose or Start Earlier with Combination Therapy? Several studies have shown that combination therapy is more effective in controlling arterial blood pressure than uptitrating to the maximal dose of an antihypertensive medication and if the goal is not reached to add an additional blood pressure lowering pill. The advantage to start with combination therapy is that the dose of each blood pressure lowering medication can be kept at a lower dose and, consequently, there is a lower risk for side effects. The simplicity of combination therapy favors fewer pills and a greater potential for therapeutic adherence as well as less expense. Moreover, we need to realize that the majority of hypertensive patients need lipid-lowering therapy and a large group also requires treatment for diabetes.

2.18.2.2.5. Do Efficacy and Adverse Effects of Hypertension Treatment Differ by Race? Randomized trials demonstrate that antihypertensive medications can control hypertension and prevent complications in African Americans and Caucasians. Meta-analyses have shown that African Americans demonstrate reduced blood pressure responses to monotherapy with β(beta)-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers, compared with diuretics or calcium channel blockers. These differences are usually eliminated by adding adequate doses of a diuretic.

There is also evidence that a DASH (Dietary Approaches to Stop Hypertension) and salt-reducing diet can have a more significant blood pressure reducing effect in African Americans compared with Caucasians.

The combination of isosorbide dinitrate with hydralazine has shown a significant effect in risk reduction in cardiovascular morbidity and mortality in heart failure in an African-American population who were already treated with the standard therapy for heart failure.

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