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RELIAS
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A Contemporary Review of Hypertension

Because of the importance and frequency of hypertension in primary care practices, we are devoting two issues to the subject. This issue focuses on the definition of blood pressure and current guidelines, risk factors, relationship to cardiovascular disease, blood pressure measurement, patient evaluation, and secondary causes. The next issue will cover treatments (pharmacological and non-pharmacological), initial therapy, relationship to various disease conditions (diabetes, ischemic heart disease, heart failure, chronic kidney disease, cerebrovascular disease, ischemic stroke, stroke prevention, atrial fibrillation, valvular heart disease, aortic regurgitation, sexual dysfunction), resistant hypertension, hypertensive crises and emergencies, preoperative management, and adherence strategies.
— Gregory R. Wise, MD, FACP, Editor

Hypertension (HTN) is a leading cause of death and morbidity worldwide.[1,2] The burden and prevalence of the disease is increasing globally. The annual rate of death and disability-adjusted life-years associated with a systolic blood pressure (SBP) ≥ 140 mmHg increased from 97.9 to 106.3 per 100,000 persons and 5.2 million to 7.8 million, respectively, between 1990 and 2015.[2] HTN also is associated with increased cardiovascular disease (CVD) risk as well as being a major cause of death in western countries.[3] In the United States, HTN is associated with more CVD deaths than any other modifiable disease condition.[4] For example, according to data from an epidemiological study, the National Health and Nutrition Examination Survey (NHANES), involving 23,272 participants, an estimated 50% of deaths from coronary heart disease (CHD) and stroke were attributable to HTN.[5] In another epidemiological cohort, the Atherosclerosis Risk in Communities study, HTN contributed to about 25% of CVD events (CHD, coronary revascularization, stroke, or heart failure).[6] HTN is also the second leading cause of end-stage renal disease (ESRD) among patients with kidney disease in the United States (34% of incident ESRD).[7]

Blood Pressure Definitions

Based on the 2017 American College of Cardiology/American Heart Association (ACC/AHA) consensus guidelines, HTN recently was redefined as blood pressure (BP) ≥ 130/80 mmHg (from a previous threshold of 140/80 mmHg).[8] However, this new definition has not received universal endorsement. The American Academy of Family Physicians and American College of Physicians have opposed these new guidelines and published their own consensus statements.[9] The new systolic BP diagnostic threshold (also a therapeutic target goal) has been the focus of contention. Opponents of the new ACC/AHA

EXECUTIVE SUMMARY

Hypertension is a common and serious condition that contributes to an estimated 40% of deaths from coronary heart disease and stroke, and is the second leading cause of end-stage renal disease.

- In 2017, the American College of Cardiology/American Heart Association issued new consensus guidelines that included a controversial redefinition of hypertension.
- Although the number of adults with uncontrolled hypertension has improved, challenges in control persist, especially for those between the ages of 18-39 years and for those older than 75 years of age.
- Out of office and self-monitoring with ambulatory blood pressure measurement is indicated in individuals with suspected white coat and masked hypertension, resistant hypertension, hypotensive symptoms with antihypertensive medications, and episodic hypertension.
- Patient evaluation focuses on identifying potentially reversible factors, seeking possible secondary causes, and assessing target organ damage.
- Although routine testing to evaluate for secondary causes of hypertension is not recommended, certain conditions indicate the advisability of an investigative workup.

guidelines contend that there may be a potential for more harm than benefit, especially among elderly patients with adoption of these strict criteria.[9] Also, they further contend that the ACC/AHA guidelines lend more weight to evidence derived from the Systolic Blood Pressure Intervention Trial (SPRINT) and less consideration of the systematic review of other scientific data. From an epidemiological standpoint, the new definition for HTN translates to a net increase in the prevalence of the HTN among U.S. adults. In a recent study, researchers estimated that the overall prevalence of HTN in the United States will increase to 45.4% of the population (105 million adults) from 32.0% (74.1 million) when compared to the 2014 guidelines.[10] Overall, the prevalence of HTN is not distributed uniformly across the U.S. population. The prevalence of HTN increases with age, and is higher among blacks than age- and sex-matched Caucasian, Asian, and Hispanic Americans.[8] The heterogeneity in the prevalence of HTN could be attributable partly to the national obesity trends as well as the increasing segment of the population that is elderly. For example, the prevalence of obesity among U.S. adults aged ≥ 20 years was 56.0% and 69.0% in the NHANES 1988-1994 and 2011-2014, respectively, and these rates correspond to HTN prevalence rates of 28.8% and 32.0% for the same period using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) BP definitions. The Framingham Heart Study reported a 90% life-time risk of developing HTN for non-hypertensive adults aged 55 or 65 years in both men and women,[11,12] while some studies estimate more than a 50% prevalence of HTN in adults aged 60 to 69 years and 75% prevalence for those aged 70 years or older.[13] The lifetime risk of developing HTN is higher among African Americans and Hispanics than whites and Asians.[12]

HTN Control in the General Population

In the last several decades, substantial progress has been made in the general awareness, treatment, and control of HTN. However, patients with HTN still have an increased risk of adverse CVD events compared to those without HTN.[5] For example, in the NHANES 2009-2012 report, prevalence estimates were 80.2% and 85.4% for awareness, 70.9% and 80.6% for treatment, 69.5% and 68.5% for control among those on therapy, and 49.3% and 55.2% for overall control in adult men and women with HTN, respectively.[14] These estimates were based on previous HTN guidelines (BP ≥ 140/90 mmHg for diagnosis and BP ≤ 140/90 mmHg for control). The number of adults with uncontrolled HTN has improved over the years, but challenges still persist, especially for those between the ages of 18 and 39 years and those ≥ 75 years of age in whom control rates are still low, 34.4% and 46%, respectively, based on data from the NHANES 2009-2012. There also are persistent and unique challenges of racial and gender disparities in the control of HTN. For example, BP control in blacks and Hispanics is disproportionately lower than in whites. Control rates among black and Hispanic men and women are 31.1% and 23.6%, respectively, and 43.3% and 52.9%, respectively, compared to 41.3% and 57.2% for white men and women, respectively, during the 2009-2012 time frame.[15] Achieving greater control of HTN is desirable from a public health standpoint to mitigate the adverse events associated with the disease. In general, about 12.3% of hypertensive U.S. adults have an average SBP ≥ 160 mmHg or average diastolic blood pressure (DBP) ≥ 100 mmHg, highlighting the critical areas for improvement given that uncontrolled HTN leads to increased incidence of preventable ischemic heart disease, kidney disease, stroke, and death.[16]

Risk Factors for Hypertension

HTN commonly occurs in individuals with other CVD risk factors. Table 1 shows modifiable and non-modifiable risk factors for the disease.

Based on data from the NHANES 2009-2012, among U.S. adults with HTN, 63.2% also had hypercholesterolemia, 49.5% were obese, 27.2% had diabetes mellitus, 15.8% had chronic kidney disease (CKD; defined as estimated glomerular filtration rate [eGFR] < 60 mL/min and/or urine albumin to creatinine

Table 1. Common Coexistent CVD Risk Factors in Patients With Hypertension

Modifiable	Relatively Non-modifiable
• Dyslipidemia • Obesity (body mass index ≥ 30 kg/m^2) • Diabetes mellitus • Active or passive cigarette smoking • Physical inactivity	• Advancing age • Family history • Male sex • Low social economic status • Psychosocial stress • Chronic kidney disease • Obstructive sleep apnea

ratio ≥ 300 mg/g), and 15.5% were also current smokers.[17] These data highlight the fact that HTN is coexistent with other CVD risk factors. The clustering of multiple CVD risk factors in patients with HTN translates into increased absolute CHD and stroke risk. A study of U.S. adults with HTN between 2009 and 2012 reported a 10-year risk of CHD > 20%, 10-20%, and < 10% for 41.7%, 40.9%, and 18.4% of all participants, respectively.[17] Hypertensive adults with two or more CVD risk factors have a significantly higher risk of CVD death, nonfatal myocardial infarction (MI), and fatal or nonfatal stroke than those with only one risk factor.[17,18] Treatment of modifiable risk factors can help prevent and/or control BP with eventual reduction in the global CVD risk burden.

Notwithstanding, some patients with HTN have underlying genetic predisposition.[19] Additionally, lifestyle factors, including high sodium intake, obesity, excessive alcohol intake, and certain medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], stimulants, and decongestants) may induce or aggravate HTN and make it difficult to control.[20,21,22]

Relationship Between BP and Cardiovascular Outcomes

Elevations in SBP and/or DBP are associated with increased CVD risk.[23,24] CVD risk is increased in a log-linear pattern from SBP < 105 mmHg to > 180 mmHg and from DBP < 75 mmHg to > 105 mmHg, according to a meta-analysis of 61 prospective trials.[23] These authors further reported a doubling of risk for death from stroke, heart disease, or other vascular disease with a rise in SBP and DBP by 20 mmHg and 10 mmHg, respectively.

An observational study involving more than 1 million adults ≥ 30 years of age reported an increased incidence in CVD, heart failure (HF), cerebrovascular accidents (CVA), peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA) with higher SBP and DBP when the two were evaluated independently.[24] These findings are consistent with observations from the Framingham Heart Study demonstrating that individuals with SBP between 130-139 mmHg and DBP between 85-89 mmHg had twice as high relative risk of cardiovascular mortality compared to those with normal BP using the JNC 7 criteria.[25] This graded dose-response relationship of BP thresholds and cardiovascular outcomes has served as the impetus for recommending more stringent HTN cutoffs (BP ≥ 130/80 mmHg) by the ACC/AHA. The rationale for this strict BP threshold is to enable identification of "normal BP" by JNC 7 guidelines in patients for whom early lifestyle intervention measures may vitiate the progression of HTN.[8,26]

Others have raised concern that the label "prehypertension" in the previous iterations of guidelines may have led to "therapeutic inertia" resulting in less care.[27] The 2017 ACC/AHA guidelines on HTN also place emphasis on reducing the global CVD risk of a patient. In this vein, the guidelines recommend estimating the 10-year risk of cardiovascular disease to allow for individualized care (http://tools.acc.org/ASCVD-Risk-Estimator/). As previously stated, there has been no universal endorsement of these guidelines. Some sections of the medical community have argued that lowering the BP threshold for diagnosis of HTN may be misinterpreted to be a mandate for unwarranted pharmacologic therapy with potential for harm in patients with minimal CVD risk.[27] Another concern is that the 10% 10-year-risk designation advocated in the ACC/AHA guidelines is not strongly supported by evidence from randomized, controlled trials (RCTs). The SPRINT trial that formed the foundation for this recommendation had enrolled patients with more comorbid conditions (15% or higher Framingham risk scores) to identify patients who would benefit from an intensive BP treatment strategy. Thus, critics contend that the sicker SPRINT trial population is not easily generalizable to the general population.[27]

In a break from the JNC 8 Expert Panel on BP, the ACC/AHA guidelines were lowered across the board even for people aged 65 years or older. A SPRINT subgroup analysis showed benefit from an intense BP control strategy, even in those 75 years of age or older, without significant differences in adverse events reported (including hypotension, syncope, and electrolyte abnormalities) between the two trial arms. There are genuine concerns for potentially serious adverse effects with intense therapy in the debilitated and frail elderly. Theoretically, elderly patients, especially those with poor vascular compliance (pulse pressures > 80-90 mmHg), may experience dizziness and poor mentation with tight BP control. Further, the new BP guidelines failed to address the challenge of diastolic HTN. As opposed to SBP, DBP elevation has not been associated consistently with increased CVD risk.[28,29] However, it is important to note that DBP < 60 mmHg in patients with diabetes and those with CAD has been associated with higher risks of progressive kidney disease and ischemic heart disease.[30] Given these considerations, a balanced approach anchored firmly on a careful assessment of patient risk and

Table 2. Comparison Between ACC-AHA and JNC 7 Classification of Hypertension

ACC-AHA			JNC 7		
BP category*	**SBP (mmHg)**	**DBP (mmHg)**	**BP category**	**SBP (mmHg)**	**DBP (mmHg)**
Normal	< 120	< 80	Normal	< 120	< 80
Elevated BP[1]	120-129	< 80			
Grade 1[a]	130-139	80-90	Prehypertension	120-139	80-90
Grade 2[b]	≥ 140	≥ 90	Grade 1 Grade 2	140-159 ≥ 160	90-99 ≥ 100

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure
*Designate to higher BP category those with both SBP and DBP elevated.
[a]Grade 1 represents a subset of individuals previously labeled prehypertensive.
[b]Grade 2 combines both grade 1 and 2 hypertension in previous guidelines (JNC 7).

strong clinical judgment is advised in the application of guidelines on HTN. Table 2 compares definitions and classification of HTN between the JNC 7 and the 2017 ACC/AHA guidelines.

Systolic and Diastolic HTN

Unlike DBP, SBP consistently has been associated with CVD risk in multiple studies.[28,29] However, some studies suggest that DBP might be a more potent risk factor for CVD than SBP in those younger than 50 years of age, following which age SBP assumes a greater role in CVD risk.[31] The aging process is associated with reduced compliance of the arterial vasculature leading to vascular stiffness.[31] For this reason, isolated SBP is common in the elderly population. The age-related increase in central arterial stiffness results in greater peripheral runoff during systole and less blood in the aorta during diastole that culminate in low DBP.[32] Therefore, aging is associated with an increase in pulse pressure (PP), the difference between SBP and DBP. Both SBP and PP are major predictors of cardiovascular mortality in people older than 60 years of age.[31] Treatment of isolated SBP reduces overall mortality, cardiovascular mortality, and development of HF.[33,34]

Measurement of BP

Obtaining accurate and valid BP measurements is essential in categorizing BP level, diagnosis, and appropriate management of HTN. BP measurements are best obtained using a well-functioning and validated BP measuring device. Concerns for mercury spillages with potential toxicity have led to increased adoption of oscillometric devices that rely primarily on sensors to detect oscillations in pulsatile blood volume during cuff inflation and deflation. Aneroid manometers and automated electronic devices now are widely available. However, these BP measuring devices must be validated and calibrated periodically. Table 3 highlights a summary of steps necessary in ensuring accurate BP measurement.[8]

Out of Office and Self-monitoring of BP

Out of office BP measurement and self-monitoring of BP allow for regular measurement of BP at home or elsewhere. Interestingly, there is evidence to suggest BP reduction is achieved readily with self-monitoring of BP in hypertensive subjects.[35,36,37] These reductions in SBP and DBP may be even more pronounced when self-monitoring is used in conjunction with other interventions. More recently, it has been observed that there are frequent discordances between office and out of office BP measurements, with some advocating for increased use of out-of-office BP measurements to ascertain correct BP measurements.[8] The two main methods commonly used for out-of-office BP measurements are home BP measurement (HBPM) and ambulatory BP measurement (ABPM). ABPM allows for BP measurement during routine daily activities and is preferred to HBPM. However, HBPM is more practical and can be reliable if the BP measuring device is validated and properly calibrated and the patient is educated on proper use. Office BP rates generally are higher than both ambulatory and home BP rates, especially in those with higher blood pressures. In general, office BP of 130/80 mmHg corresponds to HBPM BP of 130/80 mmHg and to average ABPM BPs of 130/80 mmHg, 110/65 mmHg, and 125/75 mmHg for daytime, nighttime, and 24 hours, respectively.[8] Additionally, office BP of 140/90 mmHg corresponds to HBPM BP of 135/85 mmHg and to average ABPM BPs of 135/85 mmHg, 120/70 mmHg, and 130/80 mmHg for daytime, nighttime, and 24 hours, respectively.[38,39] It is important to ensure that patients are well-educated on proper BP measuring techniques. (*See Table 3.*)

ABPM devices are programmed to obtain readings every 15 to 30 minutes throughout the day and every 15 to 60 minutes during the night. Other than providing reliable measures of BP, ABPM devices also give clinically relevant trends on nocturnal BP dipping through provision of daytime to nighttime BP ratio. The device also might help identify early-morning BP surge, 24-hour BP variability, and symptomatic hypotension. Because of this difference in office, HBPM, and ABPM BP values, different BP thresholds

Table 3. Proper Measurement of BP

Patient preparation:
- It is advised that the patient avoids caffeine, smoking, and exercise 30 minutes or more before BP measurement.
- The patient should empty his or her bladder before BP measurement.
- Have patient relax while seated in chair with both feet on floor and back fully supported for more than five minutes. Need to also ensure a quiet environment.
- The arm to which the cuff is applied should have no clothing.

Ensure proper technique for BP measurement:
- Rest patient's arm on table or desk for support.
- Middle of cuff should be at level of right atrium, and the correct cuff size should be at least 80% of patient's arm.
- Ensure BP is taken using validated and accurate device.

Proper measurement and documentation of BP:
- For manual or auscultatory methods of determining BP, the radial pulse must be palpated prior to applying cuff pressure, and the pressure at which pulse is obliterated when cuff is inflated used as an estimate for SBP. Inflation to 20-30 mmHg above this pressure, and a slow deflation (2 mmHg/sec) can be used for accurate measurement of SBP.
- The appearance of the first Korotkoff sound and the disappearance of all Korotkoff sounds correspond to SBP and DBP, respectively.
- Repeat measurements can be obtained after one to two minutes of rest.
- BP should be checked in both arms at first visit, and the arm with the higher reading used for subsequent measures.
- An average of two or more readings obtained on two or more occasions must be used to estimate a patient's level of BP.
- A patient must be provided with details of these readings.

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure
Table is consistent with the 2017 High Blood Pressure Clinical Practice Guideline.

have been advanced to categorize high BP with use of HBPM and ABPM, but general consensus still is lacking. Previously, the JNC 7 suggested diagnosis of HTN in individuals with ambulatory daytime BP ≥ 135/85 mmHg and BP ≥ 120/75 mmHg during sleep.[26] This recommendation was driven partly by evidence that individuals with average ambulatory BP readings > 135/85 mmHg have a two-fold increased incidence of cardiovascular events compared to those with BP < 135/85 mmHg.[40] ABPM is indicated in individuals with suspected white-coat and masked HTN, resistant HTN, hypotensive symptoms with antihypertensive medication, and episodic HTN.

White Coat and Masked HTN

HBPM and ABPM make further stratification of BP into several clinically useful categories possible. White coat HTN is characterized by elevated office BP, but normal readings on ABPM or HBPM. The "white coat" effect is considered significant when office SBPs/DBPs are > 20/10 mmHg than home or ambulatory SBP/DBPs. It is important to recognize white coat HTN, since it has been implicated in pseudo-resistant HTN, leads to underestimation of office BP control,[41] and can be a cause of unnecessary intensification of antihypertensive therapy. The prevalence of white coat HTN is between 13% and 35%.[42,43] White coat HTN rarely progresses to sustained HTN in those who are older and obese,[44] and has been associated with a slightly increased risk of CVD and all-cause mortality risk.[45,46,47] Conversely, masked HTN is characterized by normal office BP but elevated out-of-office (HBPM or ABPM) BP readings. Estimates from population-based surveys suggest a prevalence of 10% to 26% and 14% to 30% for masked HTN in population-based surveys and normotensive office populations, respectively.[48,49,50] However, masked HTN is associated with a two-fold increased CVD and all-cause mortality compared to that seen in normotensive individuals.[51] Thus, HBPM and ABPM serve to identify patients with white coat and masked HTN.

Masked uncontrolled HTN, an entity analogous to masked HTN, is characterized by office BP readings suggestive of adequate control but HBPM or ABPM readings that are consistently above BP goal.[52] Masked uncontrolled HTN seems to have a CVD risk profile similar to that of masked HTN,[53] but the therapeutic implications of identifying it remain unclear. It appears reasonable to screen patients with increased CVD risk or target organ damage for masked uncontrolled HTN.

Patient Evaluation

Evaluation of the patient with HTN is focused on achieving the following goals:

1. Identification of potentially reversible individual patient lifestyle risk factors, cardiovascular risk factors, and comorbid diseases;
2. Identification of potential secondary causes of HTN; and
3. Assessment of target organ damage.

The above goals also may prove useful in guiding patient management. Obtaining a detailed history and thorough physical exam might help identify potentially reversible risk factors, secondary causes, comorbid medical conditions, and complications of HTN. History might aid in differentiating between primary (essential) and secondary HTN. Some clues from a patient's history for essential HTN include a family history of HTN, advancing age, overweight/obesity, physical inactivity, and high sodium intake. Therefore, clinicians must inquire about a patient's dietary habits, physical activity, tobacco use, and alcohol use. It is also important to look for comorbid medical conditions and associated complications such as diabetes, dyslipidemia, HF, obstructive sleep apnea, CVAs, PAD,

Table 4. Secondary Causes of Hypertension

Secondary Cause	History	Physical Exam Findings	Investigations
Medications or substance use	Use of medications and other substances including oral contraceptive pills, nasal decongestants (phenylephrine, pseudoephedrine), steroids, NSAIDs, antidepressants (SNRIs, MAOIs, TCAs), atypical antipsychotics (olanzapine, clozapine), immunosuppressants (cyclosporine), tyrosine kinase inhibitors (sunitinib), angiogenesis inhibitors (bevacizumab), caffeine, alcohol, cocaine, and amphetamines (methylphenidate dexmethylphenidate, dextroamphetamine)	Nonspecific, including diaphoresis, tachycardia, and tremulousness	• Toxicology screen (urinary for illicit drugs) • Withdrawal of substance might result in improvement • Caution must be exercised as medication or substance withdrawal might precipitate serious symptoms of withdrawal
Obstructive sleep apnea	Snoring, fatigue, unrefreshing sleep, and need for frequent daytime napping, somnolence, obesity, male gender and age older than 50 years; screen with STOP-BANG questionnaire	Obesity (BMI > 30 kg/m^2), large neck circumference (> 17 inches [males] and > 15 inches [females]), kissing tonsils, high arched palate, loss of nocturnal deep in BP, nocturnal hypoxia	• Polysomnography (sleep study)
Hyperthyroidism	Palpitations, irritability, weight loss, hyperdefecation, tremors, menstrual abnormalities, skin and hair changes, and heat intolerance	Eye findings (proptosis, lid lag), thyromegaly, tremulousness, tachycardia, warm/moist palms and fine tremors	• Thyroid-stimulating hormone and free thyroxine levels Radioactive iodine uptake if hyperthyroidism confirmed
Hypothyroidism	Fatigue, slowed mentation, cold intolerance, constipation, menstrual irregularities, coarse hair, and dry skin	Coarse hair, periorbital edema, goiter, dry skin, and delayed reflexes	• Thyroid-stimulating hormone and free thyroxine levels
Hyperaldosteronism	Muscle cramps and weakness from hypokalemia; unprovoked hypokalemia in hypertensive patient	ECG changes related to hypokalemia or arrhythmias (e.g., atrial fibrillation)	• Plasma aldosterone to renin ratio after correcting hypokalemia (ensure patient is off aldosterone antagonist therapy for 4-6 weeks) • Oral sodium loading or intravenous saline infusion with measurement of 24-hour urine aldosterone or plasma aldosterone four hours after infusion, respectively • CT scan of adrenals with adrenal vein sampling as indicated

NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitors; MAOI, monoamine oxidase inhibitors; CT, computed tomography; STOP-BANG, Snoring, Tired, Observed apnea/hypopnea, BMI, Age, Neck circumference, Gender

and renal disease. Vigilance for secondary causes of HTN is key. (*See Table 4.*)

Therefore, reviewing medications and determining recreational drug use are crucial to the identification of reversible factors that might need to be addressed to help manage HTN. History can provide clues to the severity of HTN, including the presence of underlying

Table 4. Secondary Causes of Hypertension (continued)

Secondary Cause	History	Physical Exam Findings	Investigations
Cushing's syndrome	Weight gain, easy bruisibility, central obesity, facial rounding, depression	Central obesity, moon facies, buffalo hump, supraclavicular fat pad, wide violaceous striae	• Screen with overnight dexamethasone suppression test • Midnight salivary cortisol • 24-hour urinary cortisol for confirmation
Kidney disease or failure	Prior history of polycystic kidney disease, other pre-existing conditions with potential to damage kidneys, e.g., diabetes and SLE, obstructive and irritative urinary symptoms (hesitancy, frequency, urgency, poor urinary stream, dribbling, and nocturia); decreased or increased urine output; chronic analgesic use	Nonspecific, including conjunctiva pallor, abdominal mass	• Investigations tailored to assessment of renal function (BUN, Cr, GFR) and potential causes of renal disease, such as diabetes, lupus, etc. • Renal ultrasound can help identify obstruction
Renovascular disease	Resistant hypertension, abrupt onset or increasingly difficult to control hypertension, worsening renal function after initiation of ACEI or ARB	Renal artery bruits, bruits in other arterial territories (e.g., carotids, femoral arteries)	• Renal duplex, MRA, or abdominal angiogram • Selective renal intra-arterial angiography
Pheochromocytoma	Episodic headaches, palpitations, pallor, dizziness, and labile blood pressure	Pallor, tachyarrhythmias, postural hypotension, fever, tremors, pulmonary edema, abdominal mass (rarely)	• 24-hour urine metanephrines or plasma metanephrines under standard conditions • imaging of abdomen with CT/MRI
Coarctation of aorta	Typically young patient (< 30 years) with hypertension	Upper extremity BP higher than lower extremity BP, radial-radial delay, radial-femoral delay, lower extremities colder than upper extremities, continuous murmur on chest or back	• Screen with an echocardiogram • Thoracic and abdominal CT angiogram or MRA
Primary hyperparathyroidism	Incidentally discovered elevated serum calcium; also might present with abdominal pain, constipation, urinary stones, and kidney dysfunction	Usually normal, evidence of dehydration in those with severe hypercalcemia	• Serum calcium and parathyroid hormone levels
Acromegaly	Enlarging hat, glove, or shoe size, headaches, and visual disturbances	Tall stature, macrocephaly, frontal bossing, coarse facial features, large hands and feet	• Insulin-like growth factor-1 level • Pituitary MRI

SLE, systemic lupus erythematosus; ACEI, angiotensin converting enzymes inhibitor; ARB, aldosterone receptor blocker; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; BUN, blood urea nitrogen; Cr, creatinine; STOP-BANG, Snoring, Tired, Observed apnea/hypopnea, BMI, Age, Neck circumference, Gender

end-organ damage. For example, chest pain and dyspnea in a hypertensive patient may signal cardiac complications including CAD and pulmonary edema. Headaches, visual disturbances, focal weakness, and confusion might occur in individuals with hypertensive retinopathy, CVA, and hypertensive encephalopathy. The presence of target organ damage signals the need for more aggressive BP control. A physical exam must focus on identifying possible causes of HTN (*see Table 4*) while also evaluating for target organ damage. The correct measurement of BP is crucial.

Table 5. Recommended and Optional Tests for Evaluation of Patients With Hypertension

Laboratory Test		Importance
Basic	12-lead electrocardiogram (ECG)	Assess for left ventricular hypertrophy, arrhythmias such as atrial fibrillation (not uncommon in those with hyperthyroidism) and changes related to hypokalemia in those with primary or secondary hyperaldosteronism.
	Complete blood count (CBC)	Might show anemia in those with pre-existing renal disease.
	Fasting blood glucose	Hyperglycemia might be indicative of diabetes or the metabolic syndrome.
	Lipid panel	Assess for dyslipidemias.
	Urinalysis	Evidence of dysmorphic red blood cells, casts, and proteinuria (may suggest diabetic nephropathy or merely pre-existing renal disease). Urine total protein to creatinine ratio may be important in those with proteinuria.
	Renal function including GFR	Elevated creatinine and blood urea nitrogen suggest renal disease either as a complication or cause of hypertension. Level of creatinine might not be an accurate measure of renal function, especially in those with low muscle mass like the elderly and debilitated patients. However, creatinine can be used to measure creatinine clearance. Estimated GFR must be obtained.
	Serum sodium, potassium, and calcium	Elevated corrected serum calcium may suggest hyperparathyroidism. Hypokalemia in presence of metabolic alkalosis suggests mineralocorticoid excess. Help establish a baseline as levels of these electrolytes typically are affected by diuretic therapy.
	Thyroid function tests	Assess for thyroid disease as easily treatable cause of hypertension.
Optional Tests	Echocardiogram	Assessment for left ventricular hypertrophy and enlargement as well as systolic and diastolic function in those where it is indicated.*
	Uric acid	Hyperuricemia might preclude diuretic therapy.

GFR, glomerular filtration rate
*Assessment of LVH might be useful in patients aged ≤18 years, or those with evidence of long-standing and poorly controlled hypertension, secondary hypertension, and/or clinical manifestation of heart failure.

(*See Table 3.*) Upper extremity (arm) BPs must be compared to mid-thigh BPs in those with suspected coarctation of the aorta. In select patients, orthostatic hypotension must be measured correctly (a decline in SBP > 20 mmHg or DBP > 10 mmHg after one minute on movement from supine to standing position). Patients with pheochromocytoma may be orthostatic. The body mass index (BMI) and waist circumference, especially for patients of South Asian descent, both must be determined. Fundoscopy must be done to assess for retinopathy in those patients presenting with hypertensive emergency. Presence of thyromegaly in the right clinical context may point to pre-existing thyroid disease. Presence of tremors might signal hyperthyroidism. Radial and femoral pulses must be assessed (atrial fibrillation is not uncommon in patients with HTN, and presence of radio-femoral delay may suggest aortic coarctation). A displaced apical impulse and presence of an S4 gallop on cardiac exam may point to long-standing HTN complicated by left ventricular hypertrophy (LVH). Hypertensive patients whose clinical course is complicated by HF may have physical evidence of volume overload, such as jugular venous distension, S3 gallop, pulmonary edema, hepatomegaly, and lower extremity edema. It is important to elicit for carotid and abdominal bruits, as their presence may suggest renovascular HTN. A palpable flank or abdominal mass might be a clue for polycystic kidney disease. A palpable abdominal bruit may suggest AAA. The pulmonary exam might reveal pulmonary edema in patients with a hypertensive emergency. A neurological exam must be conducted, paying close attention to neurological deficits pointing to prior CVAs, ruptured aneurysms, or vascular emergencies depending on the acuity of presentation.

Laboratory Evaluation

Initial laboratory evaluation in a newly diagnosed hypertensive patient helps establish a baseline electrolyte status prior to medication use, CVD risk status, and ongoing medication monitoring for possible complications arising from therapy (e.g., renal dysfunction).

Importantly, initial evaluation may help diagnose secondary causes of HTN.[8] (*See Table 4.*)

The cost implications and lack of established effect on CVD risk reclassification and therapy preclude routine echocardiography in asymptomatic hypertensive patients. However, it must be noted that LVH as measured by electrocardiography, echocardiography, and magnetic resonance imaging is an independent predictor of CVD complications.[54] In fact, reduction in LVH may predict a reduction in CVD risk independent of BP reduction.[54] Routine testing to evaluate for secondary causes of HTN is not recommended. Evaluation for secondary causes of HTN might be necessary in those with onset of HTN at age < 30 years or > 55 years, increasing or sudden difficulty to control HTN despite prior adequate control, resistant HTN, historical or clinical clues suggestive of secondary HTN, and target organ damage disproportionate to level of BP elevation.[8] Table 5 provides a list of important investigations in newly diagnosed hypertensive patients.

Secondary Causes of HTN

Secondary HTN is defined as elevated BP in the setting of identifiable and often correctable underlying disease. The prevalence of secondary HTN previously has been estimated at 5-10%.[55]

Table 4 provides a comprehensive review of identifiable causes of HTN, including renovascular disease (5-34%), obstructive sleep apnea (25-50%), primary aldosteronism (8-20%), drug- and alcohol-related (2-4%), and renal parenchymal disease (1-2%). Rarely, secondary HTN is attributable to pheochromocytoma (0.1-0.6%), hypothyroidism (< 1%), hyperthyroidism (< 1%), Cushing's syndrome (< 0.1%), and coarctation of aorta (0.1%). Estimates on renovascular HTN are highly variable and depend on the cohort under consideration. For example, its prevalence is only 5% in those with HTN alone compared to a prevalence of 28% in those with HTN and peripheral vascular disease.[56] Furthermore, estimates of prevalence of primary aldosteronism in the general population with HTN are 8% compared to 20% in those with resistant HTN.[57]

Conclusion

HTN is a major public health problem both in the United States and globally. The attendant high mortality and morbidity associated with HTN warrant concerted efforts aimed at prompt diagnosis along with vigilant screening for comorbid conditions that synergistically raise the risk profile for cardiovascular events. Secondary HTN is not uncommon and should be sought in the right clinical context.

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CME Questions

1. Which of the following is a risk factor for hypertension?
   a. Cigarette smoking
   b. Obesity
   c. Physical inactivity
   d. All of the above
2. The ACC/AHA recently redefined hypertension as a blood pressure of ≥ 130/80 mmHg. What is the estimated prevalence of hypertension among U.S. adults aged 18 years and older based on this threshold for blood pressure diagnosis?
   a. One in two adults
   b. One in five adults
   c. One in four adults
   d. None of the above
3. A 67-year-old Caucasian woman comes in for her follow-up visit. She has a past medical history of coronary artery disease status post-stent placement to her left anterior descending (LAD) artery, peripheral vascular disease, hypertension, and hyperlipidemia. She has no complaints today. Her medications include lisinopril 40 mg daily, metoprolol succinate 100 mg daily, amlodipine 10 mg daily, hydrochlorothiazide (HCTZ) 50 mg daily, and spironolactone 50 mg daily. Her home blood pressure readings have averaged 166/114 mmHg despite addition of spironolactone two weeks ago. Vitals are normal except for an elevated blood pressure of 170/116 mmHg. Physical exam is remarkable for an S4 gallop and carotid and femoral artery bruits. What is your next best step in managing this patient's blood pressure?
   a. She needs evaluation for renovascular and other causes of secondary hypertension.
   b. Add minoxidil to her current blood pressure medicines.
   c. Refer her to a nephrologist.
   d. She requires admission for optimization of her blood pressure control.
4. A 36-year-old female comes to your office to establish primary care. She recently attended a free blood pressure and glucose check clinic and was advised to see a physician for her elevated blood pressure of 158/100 mmHg. She has no significant past medical history and has no complaints today. Her blood pressure is 130/76 mmHg, pulse rate 75/min, respiratory rate 16/min, and temperature is 36.6° C. The physical examination is unremarkable. Which of the following is true about correct measurement of blood pressure?
   a. The patient must avoid caffeine, smoking, and exercise 30 minutes or more before blood pressure measurement.
   b. Ensure a quiet environment, and have the patient relax while seated in chair with both feet on floor and back fully supported for more than five minutes.
   c. The middle of the cuff should be at the level of right the atrium, and right cuff size should be at least 80% of patient's arm. Appearance of first Korotkoff sound and disappearance of all Korotkoff sounds correspond to SBP and DBP, respectively.
   d. All of the above.
5. A 38-year-old Hispanic female comes into your office with complaints of episodic sweats, tremulousness, palpitations, headaches, and dizziness. She has visited urgent care facilities on numerous occasions and was told she has panic attacks. She has a history of anxiety disorder diagnosed four months ago, and currently is taking buspirone 7.5 mg twice daily. She notes that the buspirone has not helped her unpredictable episodic symptoms. Blood pressure is 178/110 mmHg, pulse rate 118/min, respiratory rate 24/min, and temperature is 37.1° C. She is diaphoretic and appears anxious. She has no proptosis, lid retraction, or thyromegaly. Heart sounds are tachycardic; no murmurs or rubs noted. Lungs are clear bilaterally. She also has tremors. What is your next step in the management of this patient?
   a. The patient needs referral to a psychiatrist for optimal management of her panic attacks.
   b. The patient's presentation is concerning for possible pheochromocytoma and hyperthyroidism, and she needs a workup for both conditions.
   c. Initiate patient on fluoxetine.
   d. Initiate patient on hydrochlorothiazide 25 mg daily, and reassess in two weeks.

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