

Mallory McClester Brown and Anthony J. Viera

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M.M. Brown (✉)
 Department of Family Medicine and Population Health,
 University of North Carolina, Chapel Hill, NC, USA
 e-mail: mallory_mcclester@med.unc.edu

A.J. Viera
 University of North Carolina, Chapel Hill, NC, USA
 e-mail: anthony_viera@med.unc.edu

General Principles

Hypertension is the most commonly seen condition in adult primary care practices. It affects one in three American adults over the age of 18, with women and men being nearly equally affected [1]. Data from the Framingham Heart Study have shown that patients who are normotensive at 55 years old still have a 90 % lifetime risk for developing hypertension [2]. Fortunately, treatment of hypertension reduces the risk of heart failure, stroke, myocardial infarction, chronic kidney disease, and cognitive decline. Left untreated, hypertension may lead to vascular and renal damage, which with time could become treatment resistant [3]. The percentage of people who know they have hypertension, who are treated, and who have controlled blood pressure (BP) has increased. From 2005 to 2010, nearly 82 % of adults with hypertension were aware of their status (up from 75 % in prior years), and approximately 75 % were taking medication. Nearly 53 % of these patients had controlled BP [4, 5].

Men and women between the ages of 55 and 64 are equally likely to have high BP with nearly 52 % of the population affected. Prior to this age, men are more commonly affected, and after these ages, more females are affected. Black women most commonly have hypertension (43 %), with black men following (40 %). Approximately 30 % of white men have high BP whereas 27 % of white women are affected. About 26 % of Mexican American men and women have hypertension [4, 5].

Lifestyle modifications to lower BP include weight loss (if overweight), increased physical activity, alcohol use only in moderation, reduced sodium intake, and the Dietary Approaches to Stop Hypertension (DASH) eating plan [6]. Multiple pharmacological treatments are available including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, and beta-blockers. Unfortunately, many patients do not fully adhere to the treatment plan or self-adjust

their regimens based on side effects of their medications. Clinicians also have a tendency to tolerate less than adequate BP control and not titrate BP-lowering medications. This clinical inertia plays an important role in suboptimal BP control. Overall, it is the physician's challenge to develop a plan with patients that will effectively control their BP, reduce cardiac risk factors, and manage comorbidities (e.g., diabetes) while minimizing side effects and maintaining quality of life. Treatment and the plan of care should include the patient's needs and preferences [2].

Detection and Diagnosis

The United States Preventive Services Task Force (USPSTF) recommends screening all adults over 18 for hypertension [7]. While the USPSTF previously made no recommendation as to screening interval, the Joint National Committee (JNC)-7 recommended screening adults every 2 years if BP was recorded as less than 120/80 mmHg and every 1 year for systolic BP 120–139 mmHg or diastolic BP 80–90 mmHg [6]. Recently, the USPSTF published recommendations for annual screening for adults 40 years and older and those at increased risk for high BP. Persons deemed at increased risk include those who have high-normal BP (130–139/85–89 mmHg), are overweight or obese, or are African American. Adults ages 18–39 years with normal BP (<130/85 mmHg) who do not have other risk factors should be rescreened every 3–5 years [8].

The diagnosis of hypertension should be based on at least two separately recorded elevated BP recordings. The finding of an elevated BP at an initial visit should be confirmed at a follow-up visit, preferably with at least two BP recordings separated by at least 1 min each time [9]. In a patient with a single greatly elevated BP reading in the office setting who already has hypertensive-related target organ damage, the diagnosis may be made without follow-up readings. BP should be recorded with the auscultatory or oscillometric method in a standardized fashion. Patients should

Table 1 Classification of blood pressure levels for adults

BP classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Management
Normal	<120	<80	Healthy lifestyle recommendations to maintain optimal BP
Pre-hypertension	120–139	80–89	Healthy lifestyle recommendations to try to prevent hypertension.
Stage 1 hypertension	140–159	90–99	Healthy lifestyle recommendations plus BP-lowering medication(s)
Stage 2 hypertension	≥160	≥100	

Source: Joint National Committee-7

be seated quietly for at least 5 min in a chair with their feet on the floor and arm supported at heart level. An appropriate-sized cuff (cuff bladder encircling at least 80 % of the arm) should be used to ensure accuracy [6]. Additionally, caffeine and nicotine should not be ingested within the 30 min prior to measurement. Ideally, ambulatory BP monitoring (see subsequent section) should be used to confirm the diagnosis [8], primarily to exclude white-coat hypertension.

BP level can be classified into one of several categories, as shown in Table 1. The BP category into which a patient falls can help guide treatment.

Evaluation

The evaluation of patients with newly diagnosed hypertension has three main goals: (1) assess for comorbid cardiovascular disease (CVD) risk factors, (2) investigate for potential secondary causes of hypertension, and (3) determine if the patient has any target organ damage. These goals can be addressed with a thorough medical history, physical exam, laboratory evaluation, and, if necessary, diagnostic procedures.

Medical History

The provider should ask about previously elevated BP measurements, CVD risk factors (Table 2), symptoms of or diagnosis of

Table 2 Major cardiovascular disease risk factors

Hypertension
Cigarette smoking
Obesity (body mass index >30)
Physical inactivity
Dyslipidemia
Diabetes
Microalbuminuria or GFR <60 mL/min
Age (>55 men or >65 women)
Family history of premature cardiovascular disease (1st degree male relative <55 years, female <65 years)

Source: JNC-7

secondary causes of hypertension (see below), medication (including supplement) use, and family history of hypertension and cardiovascular disease.

Physical Exam

Each patient diagnosed with hypertension should have a physical exam including more than one BP recording verified with recording in the contralateral arm in both the standing and sitting position. The exam should also include (1) calculation of the body mass index (BMI), (2) evaluation of the optic fundi, (3) exam of the neck including palpation of the thyroid gland and auscultation for carotid bruits, (4) cardiac exam, (5) lung exam, (6) abdominal examination with special attention for enlarged kidneys, masses, abdominal aortic pulsation, and abdominal or renal bruits, (7) examination

of the lower extremities for pulses and edema, and (8) a neurological evaluation.

Laboratory Tests and Diagnostic Procedures

Baseline laboratory tests may be helpful for the initial evaluation and are also important before initiating treatment. Recommended tests include serum potassium and sodium levels, blood urea nitrogen, and creatinine level. An electrocardiogram, blood glucose, hematocrit, and fasting lipid panel are also recommended, if not done previously, to help assess overall cardiovascular risk. The ECG also may reveal target organ damage in the form of left ventricular hypertrophy or prior myocardial infarction (Q waves). Optional tests include a TSH level and calcium. Tests such as a chest radiograph or echocardiogram are only recommended if indicated based on findings from history, physical exam, or ECG.

Secondary Causes

Though most cases of hypertension are considered idiopathic or primary, it is important to consider secondary causes of hypertension at the time of diagnosis. Diets high in salt and alcohol can contribute to elevated BP. Many medications can cause elevation of BP as well (Table 3). A trial of potentially offending medications (if possible), or a change in diet, may be warranted before embarking on pharmacological treatment.

The initial history, examination, and laboratory tests on rare occasions may reveal a potential secondary cause of hypertension which can be investigated (Table 4). The most common secondary causes of hypertension vary by age-group [10]. Among children, renal parenchymal disease and coarctation are most common, while among middle-aged adults, obstructive sleep apnea and aldosteronism are the most common. Further investigation for secondary causes should be completed in a stepwise fashion based on level of suspicion or concern [10].

Table 3 Drugs that may cause BP elevation

Drug	Common examples
Estrogen	Oral contraceptives, hormone replacement therapy
Herbals	Ephedra, ginseng
Illicit drugs	Amphetamines, cocaine
Non-steroidal anti-inflammatories	Ibuprofen, Naproxen
Psychiatric agents	Fluoxetine (Prozac), Lithium, Tricyclic Agents (TCAs)
Steroids	Prednisone
Sympathomimetics	Over-the-counter nasal decongestants

Table 4 Secondary causes of hypertension in adults

Aldosteronism
Atherosclerotic renal artery stenosis
Cushing Syndrome
Fibromuscular dysplasia
Obstructive sleep apnea
Pheochromocytoma
Renal Failure
Renal parenchymal disease
Thyroid dysfunction

Management

Benefits of Treatment

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40 %; myocardial infarction, 20–25 %; and heart failure, more than 50 % [11]. These data support the importance of treating patients to not only bring BP down but more importantly to prevent the morbidity and mortality associated with hypertension.

The panel members appointed to the Joint National Committee 8 (JNC 8) recently provided an evidence-based update to BP treatment goals. Per their report, in the general population aged ≥ 60 years, pharmacological treatment should be initiated to lower BP at systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg and treat to a goal systolic BP < 150 mmHg and goal diastolic BP < 90 mmHg. This recommendation is made with

Grade A (i.e., highest level) evidence. For patients <60 years of age, expert opinion recommendation is to initiate treatment with a systolic BP of ≥ 140 mmHg and treat to a goal of <140 mmHg, and grade A recommendation is to initiate pharmacological treatment to lower BP at diastolic BP ≥ 90 mmHg and treat to a goal <90 mmHg. In the population aged ≥ 18 years with chronic kidney disease (CKD) or diabetes, the recommendation is to initiate pharmacological treatment at systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg and treat to goal <140/90 mmHg [12].

Nonpharmacological Interventions

Lifestyle recommendations should be part of the management plan for all patients with hypertension. These recommendations include the DASH eating plan, reduced sodium intake, exercise, alcohol reduction, and weight loss if overweight (Table 5). For overall cardiovascular disease risk reduction, all patients who smoke should be counseled about smoking cessation and provided assistance modalities.

The DASH eating plan emphasizes intake of vegetables, fruits, and whole grains. Additionally, low-fat dairy products, poultry, fish, legumes, and nuts should be included. Diet should be rich in calcium and potassium. Intake of sweets, sugar-sweetened beverages, and red meats should be limited. Sodium intake should be no more than 2400 mg each day. Research has shown that a DASH eating plan with no more than 1600 mg sodium has effects similar to single-drug therapy [13].

Adults with elevated BP should be encouraged to engage in aerobic physical activity to lower BP. The recommendation is to include three to four sessions per week lasting an average of 40 min per session and involving moderate- to vigorous-intensity physical activity [14].

Some research has shown increased BP to be positively correlated to more than 2 oz/day of alcohol. Therefore, it is important to limit alcohol intake [15]. Alcohol should be limited to no more than 1 oz or 30 mL ethanol/day for women and no more than 2 oz (60 mL)/day for men [8].

Pharmacological Treatment

When deciding on pharmacological therapy, the individual patient characteristics including age, race, sex, family history, cardiovascular risk factors, and concomitant disease states should be considered. Additionally, the patient's ability to afford the prescribed therapy as well as their compliance must be taken into account.

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. In the population aged ≥ 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACE inhibitor or ARB to improve kidney outcomes. This recommendation applies to all CKD patients with hypertension regardless of race or diabetes status. Note that an

Table 5 Lifestyle recommendations for hypertension

Recommendation	Description	Approximate systolic BP reduction
DASH eating plan	Diet rich in fruits, vegetables, and low-fat dairy with reduced fat intake	8–14 mmHg
Exercise	Regular aerobic activity at least 30 min per day	4–9 mmHg
Reduced dietary sodium intake	Maximum 2400 mg (ideally 1600 mg) of sodium daily	2–8 mmHg
Moderate alcohol drinking	Maximum 2 oz ethanol per day for men; maximum 1 oz per day for women	2–4 mmHg
Weight loss	Achieve/maintain BMI of 18.5–24.9 kg/m ²	5–20 mmHg

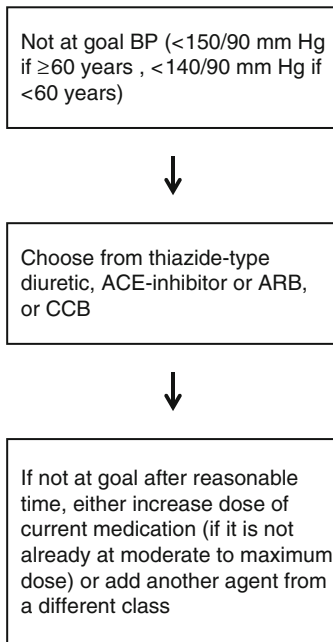


Fig. 1 Evidence-based simplified algorithm for hypertension treatment

ACE inhibitor and ARB should not be used together [16].

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, the initial drug dose should be increased or a second drug such as a thiazide-type diuretic, CCB, ACE inhibitor, or ARB should be added. If the goal BP cannot be reached with two agents, a third drug should be added [12] (Fig. 1).

Diuretics

Thiazide-type diuretics (chlorthalidone, hydrochlorothiazide) increase renal excretion of sodium and chloride at the distal segment of the renal tubule, which results in decreased plasma volume, cardiac output, and renal blood flow and increased renin activity. With these agents, potassium excretion is increased while calcium and uric acid elimination is decreased. Because of its greater potency and longer duration, chlorthalidone should be preferred over hydrochlorothiazide, especially when used alone. Potential side effects

of all thiazide-type diuretics include hyponatremia, hypokalemia, dizziness, fatigue, muscle cramps, gout attacks, and impotence. Special attention should be paid when starting these agents in patients with diabetes, elevated cholesterol, or gout as thiazides can worsen each of these conditions. None of these conditions is a contraindication, however.

Loop diuretics and potassium-sparing diuretics can be used as adjunct therapy when thiazide-type diuretics are not sufficient (e.g., in patients with decreased glomerular filtration rate). Loop diuretics (furosemide, torsemide, and bumetanide) inhibit sodium and chloride reabsorption in the proximal and distal tubules and the loop of Henle. Side effects include diarrhea, headache, blurred vision, tinnitus, muscle cramps, fatigue, or weakness. When used in high doses in patients with significant renal disease, ototoxicity may occur.

Potassium-sparing diuretics (spironolactone, triamterene, amiloride) are useful for preventing potassium wastage that occurs with thiazide and loop diuretics. Spironolactone competitively inhibits the uptake of aldosterone at the receptor site in the distal tubule, in turn reducing the effect of aldosterone. This drug is an evidence-based fourth-line medication for resistant hypertension (described below). Main adverse effects to be aware of include gynecomastia and hyperkalemia. Triamterene and amiloride are typically used more specifically to stop potassium loss, and both have side effect profiles similar to the thiazide diuretics [17].

ACE Inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II, resulting in decreased aldosterone production with subsequent increased sodium and water excretion. As a result, renal blood flow is increased, and peripheral resistance decreases. Renin and potassium levels typically increase. Major side effects include cough, angioedema, and the possibility of acute renal failure (in patients with renal artery stenosis). Importantly, this class of medication can cause

syncope in patients who are salt or volume depleted. This drug class is teratogenic in the human fetus and should therefore be avoided in pregnancy and in women who may become pregnant.

ACE inhibitors have little effect on insulin and glucose levels or lipid levels, making them a good choice for most diabetics and patients with hyperlipidemia. ACE inhibitors are a particularly good choice for patients with congestive heart failure, peripheral vascular disease, and renal insufficiency as well.

Angiotensin Receptor Antagonists

ARBs bind to the angiotensin II receptors, blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Aldosterone production decreases while plasma renin and angiotensin II levels rise. There is no notable change in the serum potassium level, renal plasma flow, glomerular filtration rate, heart rate, cholesterol level, or serum glucose.

ARBs are generally well tolerated but can cause hyperkalemia. ARBs are also teratogenic and should be avoided in women of childbearing age. The major use of ARBs is for patients who cannot tolerate an ACE inhibitor due to cough.

Calcium Channel Blockers

CCBs reduce the influx of calcium across cell membranes in myocardial and smooth muscles. This in turn dilates coronary arteries, as well as peripheral arteries. This dilation reduces total peripheral resistance leading to decreased BP. Structural differences exist between agents in this class, which lead to different adverse effect profiles as well as differences in their effect on cardiac conduction. Verapamil and diltiazem (non-dihydropyridines) work to slow the conduction through the AV node and prolong the effective refractory period in the AV node. The dihydropyridines (e.g., amlodipine, nifedipine) increase cardiac output and have a more profound

vasodilatory effect, making them the preferred CCBs for hypertension.

The main noteworthy side effect of dihydropyridine CCBs is peripheral edema, but they can also cause constipation, flushing, and tachycardia. CCBs are contraindicated in patients with heart block, acute myocardial infarction, and cardiogenic shock. CCBs have no effect on glucose metabolism or lipid levels. CCBs are a particularly good choice for patients with migraine headaches, angina, chronic obstructive pulmonary disease or asthma, peripheral vascular disease, renal insufficiency, supraventricular arrhythmias, and diabetes.

Beta-Blockers

Beta-blockers are not indicated for first-line treatment of uncomplicated hypertension but are recommended for patients following a myocardial infarction and for patients with congestive heart failure. Beta-blockers antagonize the effects of sympathetic nerve stimulation or circulating catecholamines at beta-adrenergic receptors, which are widely distributed throughout the body. Beta₁-receptors are predominant in the heart (and kidney) while beta₂-receptors are predominant in other organs such as the lung, peripheral blood vessels, and skeletal muscle. In the kidney, the blockade of B₁ receptors inhibits the release of renin from the juxtaglomerular cells and thereby reduces the activity of the renin-angiotensin-aldosterone system. In the heart, blockade of B₁ receptors in the sinoatrial (SA) node reduces heart rate, and blockade of the B₁ receptors in the myocardium decreases contractility. It is likely a combination of these effects that leads to BP reduction. The overall clinical response to beta-blockers is a decreased heart rate, decreased cardiac output, lower blood pressure, decreased renin production, and bronchiolar constriction.

The side effect profile of beta-blockers depends on their receptor selectivity. In those without intrinsic sympathomimetic activity, the heart rate is slowed, a decrease is seen in cardiac output, and an increase is noted in peripheral

vascular resistance. Bronchospasm may also be caused. Typical side effects seen with these agents include fatigue, erectile dysfunction, dyspnea, cold extremities, cough, drowsiness, and dizziness. These agents tend to increase the triglyceride level and decrease the HDL level but have little effect on blood glucose levels. Beta-blockers should not be used in patients with sinus bradycardia, second- or third-degree heart block, cardiogenic shock, and/or severe COPD/asthma.

Central Acting Drugs

Methyldopa, clonidine, guanfacine, and guanabenz are central alpha-2 agonists. These agents act to decrease dopamine and norepinephrine production in the brain, resulting in decreased sympathetic nervous activity throughout the body. BP declines with the decrease in peripheral resistance. Methyldopa is unique in its adverse effect profile as it can induce autoimmune disorders such as those with positive Coombs and antinuclear antibody (ANA) tests, hemolytic anemia, and hepatic necrosis. The other agents can lead to sedation, dry mouth, and dizziness. Importantly, abrupt clonidine withdrawal can lead to rebound hypertension.

Alpha-Blockers

Alpha-1 receptor blockers, such as prazosin, terazosin, and doxazosin, block the uptake of catecholamines by smooth muscle cells. In the peripheral vasculature, this results in vasodilation. A marked reduction in BP may be noted with the first dose of these drugs; therefore, it is recommended they be started at low doses and slowly titrated upward. Side effects of these agents include dizziness, sedation, nasal congestion, headaches, and postural effects. They have no effect on lipid levels, glucose, exercise tolerance, or electrolytes. These agents are probably best reserved for men with hypertension and comorbid BPH symptoms.

Vasodilators

Hydralazine and minoxidil dilate peripheral arterioles, resulting in a fall in BP. Several other responses simultaneously occur including a sympathetic reflex which leads to increased heart rate, renin and catecholamine release, and venous constriction. The kidneys retain sodium and water. Side effects include tachycardia, flushing, and headache. A beta-blocker and a loop diuretic are usually used with these drugs to minimize side effects. These agents are used mainly for resistant hypertension.

Follow-up and Ongoing Care

After initiating therapy, most patients should be seen monthly until BP control is met. More frequent visits should be utilized for patients with significant comorbidities or with stage 2 hypertension until BP goals are met. Once goals are met, follow-up can be spaced out to every 3–6 months. Laboratory evaluation including serum creatinine and potassium should be obtained at least 1–2 times/year [6].

Resistant Hypertension

Resistant hypertension occurs when BP remains above goal even with adherence to a combination of at least three optimally dosed antihypertensive agents of different classes. Management of resistant hypertension includes assessing adherence, readdressing lifestyle modifications, working up potential secondary causes, and optimizing drug regimens [17, 18].

It is important to revisit drug adherence in patients with resistant hypertension. Patients may discontinue the use of some agents due to side effects, multiple daily dosing, and/or financial expense. When possible, it is important to simplify the patient's medication regimen. Once-daily dosing and single-pill combinations improve patient's adherence to antihypertensive

medications [19]. Discussing side effects with the patient may increase both their understanding of the medication as well as their adherence to the agents. Volume overload can often play a role in resistant hypertension, and for this reason, unless contraindicated, all patients should be treated with a regimen that includes at least one diuretic.

It is also important to ensure accurate BP measurements when investigating resistant hypertension. Careful attention should be paid to measurement technique. Approximately one-third of patients with suspected resistant hypertension will actually have normal BP on ambulatory blood pressure monitoring. Therefore, evaluation of the patient with potentially resistant hypertension should include out-of-office monitoring to rule out white-coat effect [18].

Home and Ambulatory Blood Pressure Monitoring

With ambulatory BP monitoring (ABPM), the patient wears a monitor that is preprogrammed to measure and record the BP multiple times over 24 h. Recent recommendations from the USPSTF state that ABPM should be used to confirm high BP prior to diagnosis and treatment of hypertension, unless immediate therapy is indicated [8]. By providing confirmatory measurements in the ambulatory setting, overdiagnosis and overtreatment can be avoided.

Home blood pressure monitoring (HBPM) also can be useful in confirming the diagnosis of hypertension if done in a systemic way after BP cuff is confirmed to be the appropriate size, correct technique is used, and the device is accurate. HBPM may also improve patient's compliance with treatment and awareness of their control.

Hypertensive Emergency

A hypertensive emergency is described as a severe elevation in BP accompanied by evidence of impending or progressive target organ

dysfunction [6]. Clinical manifestations of target organ damage usually involve derangements in the neurological, cardiac, or renal systems. The patient with hypertensive emergency may present with encephalopathy, pulmonary edema, myocardial infarction, or unstable angina.

The most common origin of hypertensive emergency is an abrupt increase in BP in patients with chronic hypertension, most often as a result of medication noncompliance [20]. Hypertensive emergency may be related to medication effect. Examples include withdrawal syndrome from antihypertensives including clonidine and beta-blockers as well as stimulant intoxication with cocaine, methamphetamine, and phencyclidine (PCP). Pheochromocytoma is a rare cause of hypertensive emergency.

Upon presentation, a focused physical exam should include repeated BP recording in both arms. Direct ophthalmoscope exam should be completed with special attention to look for papilledema. A brief neurological examination should be done to assess for focal deficits and to assess for altered mental status. The cardiac and pulmonary examination should be complete with attention to possible arrhythmias and pulmonary edema. Abdominal exam should focus on palpating for abdominal masses and tenderness as well as auscultation for abdominal bruits. Peripheral pulses should be palpated.

The immediate goal when treating hypertensive emergency is to reduce the systolic BP by 10–15 %, but by no more than 25 %, within the first hour and, if the patient is then stable, to 160/100–110 mmHg over the ensuing 2–6 h [6]. Potential medication choices for treatment include hydralazine, labetalol, methyldopa, and nitroglycerin.

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