in the clinic

Hypertension

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Hypertension affects more than 65 million people in the United States, with about 2 million new cases diagnosed annually (1, 2). Most patients have primary or essential hypertension and are likely to remain hypertensive for life. Risk factors for hypertension include a family history of hypertension, African-American ethnicity, obesity, a high sodium or alcohol intake, and a sedentary lifestyle. Treatment to control blood pressure level reduces the risk for cardiovascular, cerebrovascular, and renal outcomes of hypertension. Unfortunately, many people with hypertension do not receive optimal therapy.

Screening and Prevention

What long-term health risks are associated with hypertension?
The relationship between blood pressure level and cardiovascular disease is linear, continuous, and independent of and additive to other risk factors. For persons age 40 to 70 years, each increment of either 20 mm Hg in systolic blood pressure level or 10 mm Hg in diastolic blood pressure level doubles the risk for cardiovascular disease (CVD) across the range of blood pressure levels from 115/75 mm Hg to 185/115 mm Hg (2). When other cardiovascular risk factors, such as diabetes or chronic kidney disease, are present, the CVD risk associated with hypertension is even higher. Complications of hypertension include retinopathy, cerebrovascular disease, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, and peripheral vascular disease.

What is prehypertension and what is its proper management?
Prehypertension is a category that first appeared in the seventh JNC report. Prehypertension is defined as a blood pressure level of 120/80 to 139/89 mm Hg (2). Patients with prehypertension are at increased risk for developing overt hypertension and CVD. These patients should restrict dietary sodium, lose weight, reduce alcohol intake, and increase aerobic exercise. Several trials have evaluated drug treatment for prehypertension. At present, drug therapy is not recommended for prehypertension.

The Trial of Preventing Hypertension randomly assigned participants with prehypertension to active treatment with candesartan (an angiotensin-receptor blocker (ARB)) or placebo for 2 years and followed them for 4 years. Active treatment delayed onset of hypertension but did not prevent it (4).

Trials of Hypertension Prevention (TOHP) 1 and 2 examined the benefits of reductions in weight, sodium intake, and stress and supplementation with potassium, magnesium, fish oil, and calcium in persons with diastolic blood pressure levels of 80 to 90 mm Hg. TOHP 1 suggested that weight loss (3/2–mm Hg reduction) and sodium restriction (2/1–mm Hg reduction) were effective. TOHP 2 confirmed that weight loss and sodium restriction delay hypertension (5, 6).

References:
How should clinicians diagnose and stage hypertension?
The steps in diagnosing hypertension are simple but often not followed. The most common errors (failure to have the patient sit quietly for 5 minutes before a reading is taken, failure to support the limb used to measure blood pressure, use of a too-small cuff, and too-rapid cuff deflation) lead to falsely increased readings. The best position for patients is sitting, because the studies that established the value of treating hypertension used this position to measure the blood pressures that diagnosed hypertension and guided dose adjustment (7). See Table 1 and the Box for instructions on blood pressure measurement.

A person’s blood pressure can vary widely. A single accurate measurement is a good start but not enough: Measure blood pressure twice and take the average. The running average is more important than individual readings. Hypertension is diagnosed if the average of at least 2 readings per visit obtained at 3 separate visits each 2 to 4 weeks apart is 140 mm Hg or greater systolic and 90 mm Hg or greater diastolic. According to the JNC 7, a normal blood pressure level is 120/80 mm Hg or less (2). Prehypertension is a blood pressure level of 120/80 to 139/89 mm Hg. Stage 1 hypertension is a systolic blood pressure level of 140 to 159 mm Hg or a diastolic blood pressure level of 90 to 99 mm Hg. Stage 2 hypertension is a systolic blood pressure level greater than or equal to 160 mm Hg or a diastolic blood pressure level greater than or equal to 100 mm Hg. The JNC 7 classification combines the stage 2 and 3 categories of older classifications (2). In persons older than 50 years, systolic blood pressure levels greater than 140 mm Hg are a more important CVD risk factor than diastolic hypertension.

Pseudohypertension can occur in patients with stiff, incompressible arteries. To detect it, inflate the blood pressure cuff to at least 30 mm Hg above the palpable systolic pressure and then try to “roll” the brachial or radial artery underneath your fingertips (“Osler’s

### Diagnosis

**Instructions for Taking Blood Pressure**
- Have patient relax, sitting (feet on floor, back supported) for ≥5 min before taking the blood pressure.
- Support patient’s arm (for example, resting on a desk) for the measurement.
- Use the stethoscope bell, not the diaphragm, for auscultation.
- Check blood pressure first in both arms with the patient sitting. Note which arm gives the higher reading and use this arm for all other (standing, lying down) and future readings.
- Measure blood pressure in sitting, standing, and lying positions. All measurements should be separated by 2 min.
- Use the correct cuff size and note if a larger- or smaller-than-normal cuff size is needed (Table 1).
- Record systolic (onset of first sound) and diastolic (disappearance of sound) pressures.
- Record exact results to nearest even number.

### Table 1. Blood Pressure Cuff Size Criteria

<table>
<thead>
<tr>
<th>Arm Circumference</th>
<th>Weight</th>
<th>Cuff Size to Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>24–32 cm</td>
<td>Female</td>
<td>Regular</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>33–42 cm</td>
<td>&gt;150</td>
<td>Large</td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td></td>
</tr>
<tr>
<td>38–50 cm*</td>
<td>–</td>
<td>Thigh</td>
</tr>
</tbody>
</table>

* Either cuff is acceptable for the overlap circumferences.
maneuver”) (8). Healthy arteries should not be palpable when empty. If you feel a stiff, tube-like structure, the patient may have pseudohypertension.

What is white coat hypertension? White coat hypertension is defined as an elevated office blood pressure with lower blood pressure readings measured at home or with a 24-hour ambulatory blood pressure monitor (9). The prevalence of white coat hypertension is 10% to 20% (10). These patients are at elevated risk for overt hypertension and CVD (11). Current guidelines do not recommend pharmacologic treatment for these patients but do recommend lifestyle modifications and regular follow-up.

When is ambulatory blood pressure monitoring indicated? The ambulatory blood pressure monitor is a 24-hour portable device that the patient wears during their regular activities. It measures blood pressure every 15 to 20 minutes during the day and every 30 to 60 minutes at night. Ambulatory blood pressure monitoring provides the most accurate assessment of blood pressure (10). Most patients with hypertension do not need it, and the Center for Medicare & Medicaid Services pays for only 1 indication: diagnosing white coat hypertension. The Box lists the other potential situations in which ambulatory monitoring may be helpful.

Ambulatory blood pressure monitoring may also be useful in identifying high-risk blood pressure patterns that are associated with increased cardiovascular events in patients with hypertension. One is loss of “dipping status,” which is associated with worse cardiovascular outcomes of hypertension. Blood pressure of patients with loss of dipping status falls less than 10% at night relative to daytime blood pressure, in contrast to the blood pressure of patients with dipper status, which falls at least 10% at night (12). The other high-risk pattern is blood pressure surges in the early morning hours (13), which is associated with increased cerebrovascular disease risk. A surge is generally defined as a greater than 55–mm Hg difference in systolic pressure level between sleeping and early hour waking. In these patients, physicians may wish to target treatment at the high morning systolic values.

What are the key elements of the history for patients with hypertension? Assess the duration, rapidity of onset, and severity of the hypertension. Ask about cardiovascular risk factors, concomitant medical conditions, symptoms of target organ damage, past treatment and its effects, and lifestyle (dietary habits, alcohol consumption, tobacco use, and level of physical activity). Note any family history of hypertension, renal disease, cardiovascular problems, stroke, and diabetes mellitus. Ask about increased stress, physical inactivity, and dietary salt intake.

Potential Indications for Use of Ambulatory Blood Pressure Monitoring
- Unusual variability of blood pressure level
- Possible white coat hypertension
- Evaluation of nocturnal hypertension
- Evaluation of drug-resistant hypertension
- Determining the efficacy of drug treatment over 24 hours
- Diagnosis and treatment of hypertension in pregnancy
- Evaluation of symptomatic hypotension on various medications, suggesting that the patient may be normotensive
- Evaluation of episodic hypertension or autonomic dysfunction


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headache, and sweating suggest pheochromocytoma. Muscle weakness and polyuria suggest hypokalemia from excess aldosterone. Snoring and daytime sleepiness can indicate sleep apnea, and heat intolerance and weight loss suggest hyperthyroidism.

Review current medications, including over-the-counter drugs. Ask about oral contraceptives, corticosteroids, licorice, sympathomimetics, which can increase blood pressure level, and antimigraine drugs. Nonaspirin nonsteroidal anti-inflammatory drugs can decrease the efficacy of anti-hypertensive drugs (14).

**What are the essential elements of the physical examination of patients with hypertension?**

The physical examination should look for signs of secondary causes of hypertension and end organ damage related to hypertension. Table 2 outlines key components of the examination of the patient with hypertension.

**Which laboratory tests should clinicians perform in patients with newly diagnosed hypertension?**

Newly diagnosed patients should have measurement of hemoglobin or hematocrit, serum electrolytes, serum creatinine, serum glucose, and fasting lipid levels and a urinalysis with microscopic examination and a 12-lead electrocardiogram (ECG). Additional testing may be indicated by clinical factors, suspicion of secondary causes of hypertension, and anticipated treatment.

Table 3 summarizes tests that may be useful in evaluation of possible secondary hypertension. Echocardiography is more sensitive than ECG for left-ventricular hypertrophy, which would tip the scales towards drug treatment rather than just a trial of lifestyle changes or towards true hypertension rather than white coat hypertension. If a patient has gout, check serum uric acid levels before prescribing diuretics. The presence of microalbuminuria may help to guide selection of therapy in patients with diabetes.

**Which patients should be evaluated for secondary hypertension and how should they be evaluated?**

The Box lists symptoms and signs that suggest secondary hypertension. Table 3 outlines suggested tests for secondary hypertension.

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**Table 2. Physical Examination and Key Findings in the Patient with Hypertension**

<table>
<thead>
<tr>
<th>Item</th>
<th>Routine Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance, height, weight, BMI, waist circumference, skin lesions</td>
<td>Look for signs of metabolic syndrome (overweight, abdominal obesity), skin changes can indicate rare causes of secondary hypertension (striae in Cushing syndrome, mucosal fibromas can indicate MEN II)</td>
</tr>
<tr>
<td>Funduscopy</td>
<td>Retinal changes reflect severity of hypertension: arteriolar narrowing (grade 1), arteriovenous compression (grade 2), hemorrhages or exudates (grade 3), and papilledema (grade 4)</td>
</tr>
<tr>
<td>Examination of neck</td>
<td>Assess for thyroid enlargement, carotid bruits</td>
</tr>
<tr>
<td>Cardiopulmonary examination</td>
<td>Rales and gallops may indicate heart failure, interscapular murmur during auscultation of the back can indicate renal arterial disease</td>
</tr>
<tr>
<td>Abdominal examination</td>
<td>Palpable kidneys suggest polycystic kidney disease; midepigastric bruits can indicate renal arterial disease</td>
</tr>
<tr>
<td>Neurologic examination</td>
<td>Look for evidence of previous stroke, evaluate cognition (hypertension is a risk factor for loss of cognition).</td>
</tr>
<tr>
<td>Peripheral pulses</td>
<td>Reduced leg pulses can indicate coarctation of the aorta or systemic atherosclerosis</td>
</tr>
</tbody>
</table>

*MEN = multiple endocrine neoplasia.*

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**Table 1. Symptoms and Signs that Suggest Secondary Hypertension**

- New-onset hypertension at age <25 or >55 years
- Drug-resistant hypertension (requires 3 or more drugs at maximal doses)
- Spontaneous hypokalemia
- Palpitations, headaches, and sweating
- Severe vascular disease, including coronary artery disease (CAD), carotid disease, and peripheral vascular disease
- Epigastric bruit
- Radial-femoral pulse delay, especially with an interscapular murmur.

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What are treatment goals for patients with hypertension?
See Box for blood pressure goals from different guidelines. Goal blood pressure level is less than 140/90 mm Hg. Key diseases include diabetes; chronic kidney disease; established CVD or CAD equivalents, such as acute coronary syndrome, ST elevation myocardial infarction, stroke, and stable angina (2). In patients with more than 1 g proteinuria, the recommended goal blood pressure target is 125/75 mm Hg or less.
What are the recommended lifestyle modifications for treating hypertension?

Practice guidelines recommend nonpharmacologic treatment of hypertension with lifestyle modification for all patients with hypertension and prehypertension. Although adherence to lifestyle changes can substantially lower blood pressure, these changes—and their benefits—can be difficult to maintain. Physicians must encourage patients to maintain lifestyle changes when drug therapy becomes necessary. Table 4 shows the expected effects of lifestyle modification.

Salt restriction

The effect of salt intake on blood pressure is well-established. Dietary sodium restriction can reduce systolic blood pressure level by 1 to 4 mm Hg. Dietary sodium restriction to less than 2400 mg per day is often the first lifestyle change. The average Western diet contains 3800 mg of sodium per day (15), and patients are often unaware of the high sodium content of many foods (16). Patients should especially avoid processed foods, lunchmeats, soups, Chinese food, and canned processed food.

In TOHP I, adults with diastolic blood pressure levels of 80 to 89 mm Hg and systolic blood pressure levels <160 mm Hg were randomly assigned to 18-month interventions to lose weight or to reduce dietary sodium or to 2 control groups. After 7 years, the incidence of hypertension was 18.9% in the weight loss group and 40.5% in its control group and 22.4% in the sodium reduction group and 32.9% in its control group (6).

The DASH trial randomly assigned 459 adults with systolic blood pressure levels of <160 mm Hg and diastolic blood pressure levels of 80 to 89 mm Hg and systolic blood pressure levels <160 mm Hg were randomly assigned to 18-month interventions to lose weight or to reduce dietary sodium or to 2 control groups. After 7 years, the incidence of hypertension was 18.9% in the weight loss group and 40.5% in its control group and 22.4% in the sodium reduction group and 32.9% in its control group (6).

Table 4. Lifestyle Modifications to Lower Blood Pressure Level

<table>
<thead>
<tr>
<th>Lifestyle Modification</th>
<th>Recommendation</th>
<th>Potential Decrease in SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary sodium restriction</td>
<td>Restrict dietary sodium to no more than 2400 mg/d or 100 meq/d</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Maintain normal body weight; BMI = 18.5–24.9 kg/m²</td>
<td>5–20 mm Hg per 10 kg weight loss</td>
</tr>
<tr>
<td>Aerobic exercise</td>
<td>Engage in regular aerobic exercise, aiming to do 30 min of aerobic exercise on most days of the week. It is suggested that patients walk about 1 mile per day above current activity level</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>DASH diet</td>
<td>Diet rich in fruits, vegetables, and low-fat dairy, with reduced content of saturated and total fat</td>
<td>4–14 mm Hg</td>
</tr>
<tr>
<td>Limit alcohol intake</td>
<td>No more than 2 mixed drinks, two 12-ounce cans of beer, or two 4-ounce glasses of wine daily for men and one half of this quantity for women</td>
<td>2–4 mm Hg</td>
</tr>
</tbody>
</table>

BMI = body mass index; DASH = Dietary Approaches to Stop Hypertension; SBP = systolic blood pressure

levels of 80-95 mm Hg to 8 weeks of a control diet, a diet rich in fruits and vegetables, or a “combination” diet rich in fruits, vegetables, and low-fat dairy products. The combination diet reduced systolic and diastolic blood pressure levels by 5.5 and 3.0 mm Hg more, respectively, than the control diet (P < 0.001); the fruits-and-vegetable diet reduced systolic blood pressure levels by 2.8 mm Hg more (P < 0.001) and diastolic blood pressure levels by 1.1 mm Hg more than the control diet (P = 0.07). Blood pressure reductions were larger in 133 patients with hypertension than in normotensive patients. A diet rich in fruits, vegetables, and low-fat dairy foods lowers blood pressure (17, 18).

Other lifestyle interventions
Encourage weight loss (to <20% above ideal body weight for height). Systolic blood pressure level falls approximately 1 mm Hg for every kilogram of weight loss. (19).

Encourage at least 30 minutes of aerobic exercise on most days of the week. Strongly encourage smoking cessation (it does not directly lower blood pressure but does lower cardiovascular risk). Reduce alcohol intake to no more than 2 mixed drinks, two 12–ounce cans of beer, or two 4–ounce glasses of wine daily for men and one half of this quantity for women (20, 21).

The PREMIER trial randomly assigned 810 participants to behavioral intervention (weight loss, exercise, limited sodium and alcohol intake), the DASH diet plus behavioral intervention, or one-time advice only. Relative to advice-only, systolic blood pressure levels at 6 months declined by 3.7 mm Hg (behavioral change only) and 4.3 mm Hg (behavioral change plus DASH diet) (22).

Several lifestyle changes are of doubtful value. Fish oil, magnesium, and calcium supplementation do not reduce blood pressure. Although patients may consider relaxation therapies, such as meditation and yoga, their effect is short-term (23). Caffeine may transiently increase blood pressure, but caffeine has little sustained effect on blood pressure in patients with hypertension (24).

When is antihypertensive drug therapy indicated and which drugs should clinicians prescribe as initial therapy?

Many patients with stage 1 hypertension will require drug therapy to control blood pressure despite lifestyle modification. The JNC 7 recommends starting all patients on a diuretic unless they have a compelling reason to use another drug (2). Patients with stage 2 hypertension or those requiring a greater reduction than 20/10 mm Hg to reach goal blood pressure levels should start on 2 drugs, one of which should be a diuretic.

Table 5 shows the doses, mechanisms, advantages, and disadvantages of a selection of commonly used antihypertensive drugs. The Figure provides an algorithm for treatment of hypertension, and Table 6 elaborates on compelling drug indications.

ALLHAT randomly assigned 44,000 patients age >55 years with hypertension and one additional cardiovascular risk factor to initial treatment with a diuretic (chlorothalidone), an α-blocker (doxazosin), an ACE inhibitor (lisinopril), or a calcium-channel blocker (amlodipine). Addition of a second drug was permitted as needed. The doxazosin group was discontinued when interim results showed that it could not be superior to diuretic and that heart failure was higher with doxazosin. The results with the remaining 3 drugs supported diuretics as first-choice therapy because of their efficacy in reducing cardiovascular death and nonfatal myocardial infarction, superiority in several secondary outcomes (heart failure and stroke), and low cost (25).

Clinicians should strongly consider treating hypertension in very elderly patients.

The HYVET trial randomly assigned 3845 patients older than 80 years with systolic blood pressure levels from 160 to 199 mm Hg to either placebo or diuretic (indapamide, 1.5 mg daily) with the addition of an ACE inhibitor (perindopril, 4-8 mg daily) as needed. The trial was stopped early because of the large benefit of active
How should clinicians modify choice of antihypertensive treatment based on patient characteristics and comorbid conditions?

Although diuretics are generally the recommended first-choice agent, treatment with an expected 30% reduction in fatal and nonfatal stroke and an unexpected 21% reduction in all-cause mortality. This study confirms the value of drug treatment for patients age >80 years who have systolic blood pressure levels ≥150 mm Hg (26).

Table 5. Drug Treatments for Hypertension*

<table>
<thead>
<tr>
<th>Drug Class (daily dose, mg)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Most effective in the elderly, those with isolated systolic hypertension, diabetics, and African Americans, who are likely to be salt-sensitive; inexpensive</td>
<td>May increase glucose, cholesterol, and uric acid levels; hypokalemia; photosensitivity</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Preferred for chronic kidney disease, heart failure, and diabetes. Work well with diuretics. Generic ACE inhibitors are inexpensive</td>
<td>Cough in 15% (switch to an ARB). Can accept up to 30% increase in serum creatinine with ACE inhibitors. Angioedema in 0.1%-0.7%. Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker (ARB)</td>
<td>Usually well-tolerated. Angiodema uncommon. Work well with a diuretic; Do not cause cough</td>
<td>Dizziness. Relatively expensive. Contraindicated in pregnancy</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>Carvedilol is an ß- and ß-blocker. Nebivolol is also a vasodilator. Note: Don't use ß-blockers as initial therapy except in heart failure</td>
<td>Bronchospasm, bradycardia, heart failure; masks insulin-induced hypoglycemia; impairs peripheral circulation; insomnia; fatigue; decreased exercise tolerance; hypertriglyceridemia (unless ISA present); several trials show worse outcomes with atenolol than ACE inhibitors, ARBs, and CCBs</td>
</tr>
<tr>
<td>CCBs</td>
<td>Well-tolerated and effective. Dihydropyridines, likeamlodipine, are quite potent. Relatively inexpensive</td>
<td>Diuretic-resistant edema (lesser problem if ACE inhibitor or ARB added), headache, cardiac conduction defects, constipation, gingival hypertrophy</td>
</tr>
<tr>
<td>Reserpine (0.05-0.25)</td>
<td>Inexpensive</td>
<td>Nasal congestion, depression, peptic ulcer</td>
</tr>
<tr>
<td>Central ß-agonists</td>
<td>Inexpensive</td>
<td>Sedation, dry mouth, bradycardia, withdrawal (rebound) hypertension</td>
</tr>
<tr>
<td>Guanethidine (10-50) α-blockers</td>
<td>Very potent; inexpensive</td>
<td>Postural hypotension; diarrhea</td>
</tr>
<tr>
<td>Prazosin (2-30) Doxazosin (1-16) &amp; Terazosin (1-20)</td>
<td></td>
<td>Postural hypotension; heart failure increased with doxazosin in ALLHAT</td>
</tr>
<tr>
<td>Hydralazine (50-300)</td>
<td>Inexpensive</td>
<td>Lupus reaction; headache; edema</td>
</tr>
<tr>
<td>Direct renin inhibitor Aliskiren (150-300)</td>
<td>Newly approved. Reduced plasma renin could be therapeutic per se; effective in combination</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; ISA = irregular spiking activity.

*For a full listing of drugs, see Oral Antihypertensive Drug Treatment table in PIER hypertension module.
clinicians should modify drug selection on the basis of patient characteristics and comorbid conditions. Elderly and African-American patients tend to be salt-sensitive and respond well to diuretics.
Younger patients with hypertension often respond well to suppression of the renin-angiotensin system and an ACE inhibitor or ARB may be a good initial choice for these patients. ACE inhibitors are helpful in patients with diabetes, particularly if microalbuminuria is present. Patients with heart failure can benefit from ACE inhibitors, diuretics, cardioselective β-blockers, and ARBs. β-blockers and ACE inhibitors are good antihypertensive agents for patients who have had a myocardial infarction. Patients with renal insufficiency can benefit from ACE inhibitors, particularly if proteinuria is present.

The HOPE trial randomly assigned more than 9000 patients >55 years old with CVD to ramipril 10 mg at night or placebo and found that those on ramipril had less morbidity and mortality than those on placebo. Because one half of the patients also had hypertension, the authors concluded that an ACE inhibitor is reasonable initial hypertension therapy in patients with vascular disease (27).

In the ASCOT trial, more than 19 000 adults with hypertension and 3 or more CVD risk factors were randomly assigned to either a β-blocker plus a thiazide-type diuretic (if needed) or to a combination of a calcium-channel blocker (amlodipine) and an ACE inhibitor (perindopril) if needed and, in a factorial design, to either a statin or placebo. After median follow-up of 5.5 years, the trial was stopped because cardiovascular events and total mortality were significantly lower in the group that received the amlodipine-based regimen. Although blood pressure level was well-controlled in both groups, it was lower in the amlodipine group by an average difference of 2.7/1.9 mm Hg. The amlodipine and ACE inhibitor drug combination reduced the risk for stroke by about 25%, for coronary events and procedures by 15%, and for cardiovascular deaths by 25% (28).

What is the role of combination therapies for hypertension?
Combination therapies are gaining popularity. They have several advantages, including better medication adherence. Whether they ultimately cost less for patients than individual prescriptions for each of the drugs depends on the patients’ insurance programs.

ACE inhibitors or ARBs combined with hydrochlorothiazide
Many different ACE inhibitors and ARBs are available in combination with a thiazide. This combination is well-tolerated and is often good initial therapy for stage 2 hypertension.

ACE inhibitors and ARBs combined with dihydropyridine calcium-channel blockers
An ACE inhibitor with amlodipine is available in various doses, including generics. ARBs are not available as generics. Adding an ACE inhibitor or ARB avoids the edema of amlodipine monotherapy.

ACE–ARB combination therapy
ACE–ARB combinations do not seem to have advantages. The recent ONTARGET (Ongoing Telmisartan Alone and in Combination with

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Table 7. Drug Therapy for Specific Disease Mechanisms of Hypertension*

<table>
<thead>
<tr>
<th>Disease Mechanism</th>
<th>Specific Disease Mechanisms of Hypertension*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload</td>
<td>Thiazide; loop diuretic; aldosterone antagonist</td>
<td></td>
</tr>
<tr>
<td>Sympathetic overactivity</td>
<td>β-blocker</td>
<td>Use to counteract reflex tachycardia from vasodilators or in heart failure</td>
</tr>
<tr>
<td>Increased vascular resistance</td>
<td>Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker</td>
<td>Use in heart failure</td>
</tr>
<tr>
<td>Smooth-muscle contraction</td>
<td>Dihydropyridine calcium-channel blockers; β-blockers; hydralazine</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from reference 33.

Ramipril Global Endpoint Trial study confirms that ACE inhibitors and ARBs are not additive in combination therapy for hypertension and have more side effects, such as hyperkalemia and slight decline in glomerular filtration rate (29). ACE inhibitor, ARB, and ACE–ARB combination had the same effect on cardiovascular events.

**When blood pressure is poorly controlled, how should clinicians decide between increasing dose, adding an additional agent, or switching to another drug class?**

When blood pressure is poorly controlled, it is important to avoid clinical inertia (30). The following principles were formulated to deal with a particular form of poorly controlled blood pressure called “resistant hypertension,” but they are useful whenever the blood pressure is above the target level. Resistant hypertension is when the blood pressure is above the target level on a rational, full-dose, triple-drug regimen that includes a diuretic (31, 32). If the patient has no target organ damage, consider ambulatory blood pressure monitoring to see if the white coat effect is a contributing factor. Ask about co-medication with blood pressure–raising drugs and excessive alcohol or salt intake. Reconsider secondary causes of hypertension as they are much more common in resistant hypertension. Poor adherence is also common, so carefully evaluate adherence before changing treatment.

Because volume overload is common, start treating uncontrolled hypertension by adding or increasing diuretic therapy with a thiazide (with normal renal function) or a loop diuretic (with abnormal renal function). A key to success is using several different drugs, each of which attacks a different disease mechanism. Table 7 shows physiologic mechanisms and the drug class that counteracts each. If the patient is taking 2 drugs that attack the same disease mechanism, replace 1 of them with a drug from a different class. If patient is taking 3 drugs and blood pressure remains uncontrolled, ensure that the patient is taking drugs from different classes. Consider adding a potassium-sparing diuretic, such as aldactone or amiloride, in patients taking 3 to 4 drugs if blood pressure is still uncontrolled. Consider a combined α- and β-blocker, a centrally acting agent, or reserpine (in low doses). If control remains elusive, consider consulting a specialist in hypertension management.

**How often should patients with hypertension be seen?**

Blood pressure levels and clinical judgment should guide decisions about the frequency of monitoring blood pressure. Suggested recheck intervals for blood pressure levels 140/90 to 159/99 mm Hg are 2 months, and within 1 month if levels are higher. If the systolic and diastolic blood pressure levels fall into different categories, follow recommendations for the shorter follow-up time. After adjusting medications, allow 2 to 4 weeks for the blood pressure level to stabilize before modifying therapy. Clinical opinion rather than evidence determines the interval for seeing patients with stable, well-controlled hypertension; 6- to 12-month intervals are typical practice.

**What is the value of home blood pressure level monitoring?**

Home blood pressure monitoring is a relatively inexpensive way to monitor blood pressure levels, especially before and after changing therapy. Measurements of home blood pressure levels are more accurate than office blood pressure levels (33). Some patients become obsessed with their blood pressure level, and the physician may have to set limits on how often they take home blood pressure readings, lest
their anxiety over the results raise their blood pressure level. Instruct patients on correct technique of taking blood pressure level and ask them to keep a journal in which they chart their blood pressure level once to twice daily.

Home blood pressure level monitoring can help to confirm a diagnosis of hypertension in an untreated patient (34, 35). Instruct the patient to check at least 2 readings on at least 3 (preferably 7) consecutive days in the morning between 6 and 10 a.m. and to repeat them in the evening between 6 and 10 p.m. If the average home blood pressure level is less than 125/76 mm Hg (after dropping the first day’s values), hypertension is very unlikely in an untreated person (36). Average untreated home blood pressure levels of 135/85 mm Hg and higher suggest hypertension. In-between values are an indication for further evaluation by ambulatory blood pressure monitoring.

When should clinicians consider hospitalization or referral to a hypertension specialist? The main indication for hospitalization because of elevated blood pressure is a hypertensive crisis (see Box). Indications to refer to a hypertension specialist include the following: drug-resistant hypertension uncontrolled on 3 or more drugs; uncertainty about how to evaluate or manage suspected secondary hypertension—especially pheochromocytoma or primary hyperaldosteronism—or assistance needed to assess the extent of target organ damage.

When patients present with markedly elevated blood pressure levels, how should clinicians distinguish between a hypertensive emergency and a pseudocrisis? A sudden rise in blood pressure level is classified as either hypertensive urgency or a hypertensive emergency (37). Hypertensive urgency is defined as an elevated blood pressure level greater than 180/110 mm Hg without target organ damage. Patients can usually be managed with oral medications as outpatients and sent home after a few hours of observation. A hypertensive emergency is defined as an elevated blood pressure level with impending or acute progressive target organ damage. These patients usually require admission to an intensive care unit and intravenous medication to lower blood pressure level (38). Several drugs lower blood pressure quickly. The choice depends on the physician’s level of comfort and experience with the drugs. See the Box for situations in which severe hypertension constitutes a crisis.

Situations in which Severe Hypertension Constitutes a Crisis

**Cardiovascular**
- Left-ventricular failure
- Myocardial infarction
- Unstable angina
- Aortic dissection
- After vascular surgery or coronary artery bypass grafting

**Neurologic**
- Hypertensive encephalopathy
- Subarachnoid or intracranial hemorrhage
- Thrombotic stroke

**Other**
- Severe catecholamine excess, such as clonidine withdrawal, pheochromocytoma, tyramine-MAOI* interaction, or intoxication (cocaine, phenylcyclidine, phenylpropanolamine)
- Eclampsia in pregnancy

*MAOI = monoamine oxidase inhibitors.

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**Treatment...** The goal blood pressure level should be less than 140/90 mm Hg unless the patient has other cardiovascular risk factors or diabetes, which lowers the target to less than 130/80 mm Hg. Lifestyle modifications can lower the blood pressure level, but most patients also need at least 1 drug to reach goal blood pressure. A diuretic is a good choice for initial therapy absent a compelling indication for another drug (for example, vascular disease is a strong indication to start with an ACE inhibitor). Failure to reach target blood pressure level on a near-maximal dose of one or more drugs is an indication to add a drug that attacks another mechanism for hypertension. Severe hypertension requires urgent treatment, often in the hospital, if acute cardiovascular or neurologic events are present, if the patient is pregnant, or if severe catecholamine excess is present.

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**CLINICAL BOTTOM LINE**
How many patients with hypertension receive treatment, and how well is hypertension controlled in the United States?

Of the one third of U.S. adults that have hypertension, only two thirds are aware of their hypertension, and approximately 55% are on treatment. Hypertension control rates are improving: The blood pressure level control rate was 29.2% ± 2.3% in 1999 to 2000 and 36.8% ± 2.3% in 2003 to 2004 (1). The control rates increased substantially in both sexes, non-Hispanic blacks, and Mexican Americans. Among the group of patients age 60 years and older, awareness, treatment, and control rates have all increased significantly (1). Among treated patients with hypertension, control rates approach 65%.

What do professional organizations recommend about the management of patients with hypertension?

The advice in this In The Clinic article generally represents the recommendations of the JNC 7 (2), the American Heart Association, the National Kidney Foundation, and the American College of Physicians. Links to the guidelines are listed in the Toolkit.

PIER Modules

PIER has a list of practice measures, including those of the Physician Quality Reporting Initiative (PQRI). Hypertension quality measures appear under Endocrinology, Diabetes, and Metabolism and under Nephrology.

Patient Education Resources

Access the Patient Information material that appears on the following page for duplication and distribution to patients.

Practice Measures

Practice measures from the Physicians’ Consortium for Performance Improvement (PCPI). Among the tools is a good flow sheet for recording key data over time.

Guidelines

Guidelines from the American Heart Association for managing hypertension to prevent atherosclerotic cardiovascular disease.

Guidelines from the National Kidney Foundation for managing hypertension in patients with renal disease.

ACP Guidelines for the care of hypertension in patients with diabetes.
THINGS PEOPLE SHOULD KNOW ABOUT HYPERTENSION

- Hypertension, often called high blood pressure, is a common health problem.

- Most people do not know they have high blood pressure. Some people get headaches or swollen legs due to problems related to hypertension, such as heart failure.

- We don’t know what causes hypertension. In a few people who have another disease that causes hypertension, it can be cured. But most people must take medicines to control their blood pressure.

- If you don’t get treated for your hypertension, there is a better chance you could have a heart attack, stroke, or kidney failure.

- Just having healthy habits may lower your blood pressure. Follow these healthy habits even if you take blood pressure medicine: Eat less salt, exercise more, eat more fruits and vegetables, lose weight, drink less alcohol, and stop smoking.

- Work with your doctor to have better health habits, measure your blood pressure at home, and take your medicine every day. Keep all of your doctor appointments.

For More Information

American College of Physicians: ACP Special Report: Living with Hypertension

American Heart Association: High Blood Pressure
www.americanheart.org/presenter.jhtml?identifier=2114

National Heart, Lung, and Blood Institute: Your Guide to Lowering Blood Pressure

National Kidney Foundation: High Blood Pressure (Hypertension)
www.kidney.org/atoz/atozTopic.cfm?topic=1
A 58-year-old man has had hypertension for 5 years. He has maintained a blood pressure of 135/85 mm Hg with use of hydrochlorothiazide, 25 mg/d. Laboratory assessment reveals a serum sodium level of 141 meq/L, serum potassium level of 4.1 meq/L, and fasting plasma glucose level of 132 mg/dL. These values are confirmed on remeasurement several days later.

What is the most appropriate management of this patient’s hypertension?

A. Continue the current therapy, with a target blood pressure less than 140/90 mm Hg
B. Discontinue hydrochlorothiazide therapy and begin ramipril therapy
C. Add amlodipine to hydrochlorothiazide therapy
D. Add ramipril to hydrochlorothiazide therapy
E. Increase the hydrochlorothiazide dosage to 50 mg/d

Blood pressure is 160/100 mm Hg, pulse rate is 80 per min and regular, and respiration rate is 18 per min. There is an S4 gallop and trace pretibial edema. The left leg ankle–brachial index is 0.8. Electrocardiogram shows left ventricular hypertrophy, by voltage criteria. What is the most likely diagnosis?

A. Volume and potassium depletion secondary to chronic overdiuresis
B. Pheochromocytoma
C. Primary aldosteronism
D. Severe essential hypertension
E. The Bartter syndrome

A 58-year-old man who has longstanding diabetes mellitus and peripheral vascular disease involving the left leg comes to your office for a routine follow-up visit. He has intermittent claudication when he plays golf. He is obese, with a body mass index of 40 kg/m², and is sedentary. However, he works and is apparently compliant with his medication regimen. He was taking simvastatin, 40 mg/d, last year, but discontinued this medication because of diffuse muscle and joint aches that have since resolved. He takes rosiglitazone, 4 mg/d; atenolol, 50 mg/d; hydrochlorothiazide, 50 mg/d; and aspirin, 80 mg/d. You suggest smoking cessation, weight loss, and physical conditioning.

Which of the following interventions would prevent the progression of complications of diabetes and atherosclerosis in this patient?

A. Prescribe a nonstatin lipid-lowering agent
B. Recommend vitamin E, 500 IU/d
C. Substitute insulin for rosiglitazone
D. Start treatment with amlodipine
E. Start treatment with ramipril

A 58-year-old woman is hospitalized with palpitations and shortness of breath. She has a history of hypertension and chronic atrial fibrillation, and her medications include furosemide, candesartan, and warfarin. On physical examination, the heart rate is 120 bpm with an irregularly irregular rhythm, and blood pressure is 130/80 mm Hg; she has an elevated jugular venous pulse, crackles in both lungs, and marked lower extremity edema. Echocardiography shows left ventricular hypertrophy, an ejection fraction of 70%, and no significant valvular disease. She is treated with intravenous diuretics, with improvement in her symptoms and resolution of peripheral edema and of crackles on lung examination. Her heart rate is now 99 bpm and her blood pressure is 120/75 mm Hg.

Which of the following would be the most appropriate medication to add?

A. Lisinopril
B. Spironolactone
C. Amlodipine
D. Metoprolol
E. Hydrochlorothiazide

A 68-year-old woman is hospitalized with a history of hypertension for 5 years. She has maintained a blood pressure of 130/85 mm Hg; she is now 99 bpm and her blood pressure is 120/75 mm Hg.

Which of the following would prevent the progression of complications of diabetes and atherosclerosis in this patient?

A. Prescribe a nonstatin lipid-lowering agent
B. Recommend vitamin E, 500 IU/d
C. Substitute insulin for rosiglitazone
D. Start treatment with amlodipine
E. Start treatment with ramipril