Cardiovascular Risk Factors: Hypertension

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INTRODUCTION

Hypertension affects nearly 1 in 3 individuals aged 35 to 64 years in the United States. A substantial number of individuals are unaware that they have hypertension, and an even larger number has high-normal blood pressure and is at risk for developing hypertension. This situation threatens to grow far worse as the population ages unless effective, population-based efforts to lower blood pressure are undertaken.

The National High Blood Pressure Education Program has advocated measures to increase awareness about hypertension and to enhance prevention, detection, and treatment of high blood pressure in the U.S. population. To achieve these goals and provide guidance based on recent published evidence, a Joint National Committee (JNC) has been convened approximately every 4 to 5 years since 1972. The most recent report of this expert panel (JNC 7) was issued in 2003, the primary findings of which are summarized in Table 1. The European Society of Hypertension, British Hypertension Society, and Canadian Hypertension Education Program also have issued recent guidelines that arrived at similar conclusions.

In this manual, 2 patients are used to frame a discussion of current recommendations for classifying blood pressure, evaluating patients newly diagnosed with hypertension, and preventing and treating high blood pressure. Although the case patients present with additional cardiovascular risk factors, the clinical management is focused on addressing the patient’s blood pressure risk.

BLOOD PRESSURE AND CARDIOVASCULAR RISK

Observations from epidemiologic studies show a continuous, independent, and predictive relationship between systolic and diastolic blood pressures and risk for cardiovascular disease. As blood pressure rises, so does the chance of developing stroke, myocardial infarction, heart failure, coronary heart disease (CHD), and end-stage renal disease.

A large proportion of cardiovascular disease occurs in individuals whose blood pressure is above optimal levels but not so high as to be diagnosed as hypertension. The risk for cardiovascular events is determined by the blood pressure level and the presence or absence of risk factors and target organ damage. Although the absolute risk for cardiovascular disease as a consequence of hypertension varies in different populations around the world, the relative risk does not—hypertension doubles the risk of death from CHD. Individuals who carry the highest risk for cardiovascular events are those with manifestations of target organ damage, diabetes mellitus, or isolated systolic hypertension.

The primary goal of antihypertensive therapy is to reduce the complications of hypertension. However, while many more individuals are aware that they have hypertension, the percentage of patients who are adequately controlled (ie, with blood pressure < 140/90 mm Hg) is still disturbingly low (< 30%). A large portion of the population has yet to achieve the benefits from more aggressive blood pressure lowering, particularly when risk factors for cardiovascular disease are present. This public health problem is not merely an issue of access to care. Indeed, most patients with uncontrolled hypertension are actively enrolled in care with a physician and have medical insurance. Thus, physicians need to be more aggressive in identifying patients at risk and treating to appropriate target levels of blood pressure that are associated with significant risk reduction.

HYPERTENSION DIAGNOSIS AND EVALUATION

CASE 1 PRESENTATION

A 38-year-old African American woman is seen by an endocrinologist for subclinical hypothyroidism.

History

Three months ago, as part of a routine health screening, the patient was found to have a modestly elevated thyroid-stimulating hormone level of 5.5 µU/mL (normal, 0.5–5.0 µU/mL) with a free thyroxine level of 1.1 ng/dL (normal, 0.8–1.8 ng/dL). The patient is
concerned that hypothyroidism is the cause of her weight gain over the last 5 years (11 kg [24 lb]). She has no specific symptoms referable to thyroid hormone deficiency and is otherwise well, with no significant medical or surgical history. Family history is remarkable for hypothyroidism (mother) and for hypertension and obesity (mother, father, and brother). The patient’s father developed end-stage renal disease 2 years ago, attributed to hypertensive nephrosclerosis.

The patient works as an administrative assistant and has 3 children, 2 of whom are overweight. Due to their hectic schedule, she and her family eat their meals on-the-run. She also admits that she never exercises, although at one time she routinely went to a health club. When the club membership lapsed more than 3 years ago, she decided not to renew it. She does not smoke and rarely drinks alcohol.

Physical Examination

The patient is 165 cm (65”) in height and weighs 82.7 kg (182 lb), with a body mass index (BMI) of 30.4 kg/m² and waist circumference of 99.1 cm (39”). Blood pressure is 158/86 mm Hg in the right arm while seated, and pulse is 82 bpm. The heart and vascular examination is normal. The patient’s thyroid gland is small. The remainder of the examination reveals no abnormal findings.

Laboratory Examination

Laboratory studies performed earlier in the week showed that the patient’s thyroid-stimulating hormone level was normal (3.3 µU/mL). Electrolytes, tests of liver and kidney function, and complete blood count also were normal. Other findings on fasting blood testing included:

- Blood glucose concentration, 106 mg/dL
- Total cholesterol, 253 mg/dL
- Triglycerides, 364 mg/dL
- Low-density lipoprotein (LDL), 135 mg/dL
- High-density lipoprotein (HDL), 45 mg/dL

What should be the next step in the care of this patient?

This patient’s physical examination and laboratory findings suggest a normal thyroid gland and normal thyroid function and argue against hypothyroidism as a cause of her weight gain. However, the clinical examination thus far reveals several features of metabolic syndrome (elevated blood pressure, obesity, increased waist circumference, hypertriglyceridemia, low HDL). An appropriate next step in the care of this patient would be to apply current clinical guidelines for managing her blood pressure.

Table 1. Primary Findings of the JNC 7

<table>
<thead>
<tr>
<th>Finding</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among patients older than 50 years, systolic BP &gt; 140 mm Hg is a more significant risk factor for CVD than diastolic BP.</td>
<td></td>
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<tr>
<td>Beginning at a BP of 115/75 mm Hg, risk of CVD doubles with each increment of 20/10 mm Hg.</td>
<td></td>
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<tr>
<td>Patients with a systolic BP of 120–139 mm Hg or a diastolic BP of 80–89 mm Hg should be considered as prehypertensive and require healthy lifestyle changes to prevent CVD.</td>
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<tr>
<td>Thiazide diuretics (alone or combined with drugs from other classes) should be considered first-line drug therapy for most patients with uncomplicated hypertension. However, certain coexisting conditions are compelling indications for the initial use of other antihypertensive drug classes.</td>
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</tr>
<tr>
<td>Most patients with hypertension will require at least 2 antihypertensive drugs to achieve goal BP (ie, &lt; 140/90 mm Hg or &lt; 130/80 mm Hg in those with diabetes or chronic kidney disease).</td>
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<tr>
<td>In patients diagnosed with BP &gt; 20/10 mm Hg above goal, consideration should be given to starting drug therapy with 2 agents (one typically being a thiazide diuretic).</td>
<td></td>
</tr>
<tr>
<td>Patient motivation is key to effective BP control and will be enhanced by patient trust in their physician. Empathy builds trust and is a strong motivator.</td>
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</tr>
</tbody>
</table>

BP = blood pressure; CVD = cardiovascular disease; JNC 7 = Seventh Report of the Joint National Committee. (Adapted from Chobanian et al.)

and other cardiovascular risk factors in an effort to lower her overall cardiovascular risk.

CLASSIFYING BLOOD PRESSURE

Physicians and their assistants should apply appropriate techniques in measuring blood pressure. This assures that clinical decision making is based on reliable data. Once appropriate measurements are obtained, blood pressure management begins with an appropriate classification scheme. A concept first developed in earlier guidelines was the definition of optimal, normal, and high-normal blood pressure. In recognition of blood pressure elevation as a continuum of risk for both systolic and diastolic blood pressures, the JNC 7 recommended a classification scheme wherein optimal blood pressure is renamed normal, and normal and high-normal blood pressure are considered to be prehypertension. The term prehypertension is not intended to define a disease category but rather to identify individuals who are at increased risk for developing hypertension.

In the JNC 7 classification scheme, a staging system (stage 1 or stage 2) is used to define level of hypertension,
with the higher stage being one in which combinations of medications usually are necessary to adequately control blood pressure. Stage 1 hypertension is defined as systolic blood pressure from 140 to 159 mm Hg and/or diastolic blood pressure from 90 to 99 mm Hg or, alternatively, blood pressure less than 20/10 mm Hg from the target level of less than 140/90 mm Hg. Stage 2 hypertension is defined as systolic blood pressure of 160 mm Hg or greater and/or diastolic blood pressure of 100 mm Hg or greater.

Many clinicians have continued to use more descriptive terms to describe hypertension, such as mild, moderate, or severe. Because most affected individuals fall into the category previously termed mild, these patients may not fully appreciate the significance of risk associated with what they perceive as a mild disease and, thus, may receive mixed messages about the importance of adherence to treatment. To avoid confusion between physicians and patients as to risk associated with hypertension, it is best to describe the degree of blood pressure elevation using a staging system rather than one that uses descriptors.

When systolic and diastolic blood pressures fall into different categories, the higher measurement should be used to classify the patient’s blood pressure because both are independent risk factors for subsequent cardiovascular events. Thus, the case patient’s blood pressure would be accurately classified as stage 1 hypertension. Systolic hypertension, typically associated with a widened pulse pressure, is an independent risk factor for cardiovascular disease. Indeed, in individuals older than age 50 years, the risks associated with systolic hypertension exceed those for diastolic hypertension.

- Is any further information needed before proceeding with a management plan to address this patient’s increased blood pressure?

**EVALUATION OF THE PATIENT WITH HIGH BLOOD PRESSURE**

Patients presenting with above-normal blood pressure should be evaluated with the following goals in mind: (1) verifying blood pressure elevation, (2) identifying contributors to hypertension (ie, risk factors for essential hypertension or possible secondary causes), (3) assessing lifestyle and other factors that may be contributing to cardiovascular risk, and (4) determining the extent of target organ damage.

**Assessment for Secondary Causes of Hypertension**

During evaluation, some patients may manifest signs and/or symptoms suggestive of an identifiable cause of hypertension. Secondary causes of high blood pressure include certain medications (eg, adrenal steroids, oral contraceptives, sympathomimetic agents, nonsteroidal anti-inflammatory agents), chronic kidney or renovascular disease, primary aldosteronism, pheochromocytoma, thyroid or parathyroid disease, sleep apnea, and coartation of the aorta. Additional diagnostic tests may be appropriate to evaluate individuals in whom age of onset, medical history, examination (including stage of hypertension), or initial laboratory testing suggests an underlying cause.

**Cardiovascular Risk Stratification**

The risk of cardiovascular disease is determined not only by blood pressure level but also by the presence or absence of other major cardiovascular risk factors as well as any target organ damage. The major cardiovascular risk factors for patients with hypertension include age (> 55 years for men, > 65 years for women), family history of premature cardiovascular disease (< 55 years for men, < 65 years for women), reduced glomerular filtration rate (< 60 mL/min), microalbuminuria, obesity (BMI ≥ 30 kg/m²), physical inactivity, tobacco use, dyslipidemia (elevated LDL and/or low HDL), and diabetes mellitus. Each of these factors can independently modify the risk for cardiovascular disease. Patients manifesting target organ damage as evidenced by the presence of CHD, stroke, nephropathy, peripheral vascular disease, or retinopathy are at greatest risk for subsequent cardiovascular events.

**INITIATING THERAPY FOR HYPERTENSION**

**CASE 1 CONTINUED**

The endocrinologist tells the patient that her laboratory tests and clinical examination reveal no current evidence of hypothyroidism. She notes, however, that the patient does have metabolic syndrome. She explains the components of this syndrome and emphasizes that the patient’s increased weight and blood pressure are important risk factors for cardiovascular disease that may be improved with regular aerobic exercise and a healthy diet. The physician then rechecks the patient’s blood pressure, which is 156/84 mm Hg in the right arm while seated. She recommends that the patient return in 2 weeks for another blood pressure measurement to confirm today’s readings.

At the second visit, the patient’s blood pressure is 154/84 mm Hg in the right arm while seated. Having ruled out the possibility of a secondary cause for increased blood pressure, based on the patient’s history, physical examination, and laboratory findings, the
physician makes a presumptive diagnosis of essential hypertension. She informs the patient that her levels are consistent with “stage 1 hypertension,” making it appropriate to embark on a treatment plan to reduce her blood pressure. She notes that the patient should continue to have her blood pressure checked over the next several months to confirm that she is truly hypertensive.

- **What would be appropriate initial treatment for this patient?**

**LIFESTYLE MODIFICATIONS**

A trial of lifestyle modifications would be an appropriate first step in managing stage 1 hypertension in an individual who is otherwise at low risk due to the absence of other concomitant diseases or target organ damage, such as the case patient. Successful implementation of lifestyle changes may have significant impact on the patient’s blood pressure as well as her other cardiovascular risk factors (obesity, lipid abnormalities).

Major lifestyle modifications that have been shown to be beneficial for lowering blood pressure include weight reduction (for overweight individuals), adoption of the DASH (Dietary Approaches to Stop Hypertension) diet, dietary sodium reduction, regular aerobic exercise, moderate alcohol consumption, and smoking cessation. Such lifestyle changes are key to preventing the onset of hypertension and are a cornerstone of initial treatment for patients who present with hypertension. In some cases, effective lifestyle modifications may allow subsequent medication withdrawal with maintenance of goal blood pressure levels.

**Weight Reduction**

Weight reduction has long been advocated to lower blood pressure and to reduce other cardiovascular risk factors. Weight loss has been explored in relationship to blood pressure in recent trials.21-25 In each of these trials, weight loss—particularly among obese participants—lowered blood pressure, prevented the development of hypertension, or potentiated the effect of antihypertensive medications. Results from a few of these trials are highlighted here.

Phase 1 of the Trials of Hypertension Prevention (TOHP) was an 18-month lifestyle modification trial in which individuals with high-normal blood pressure were randomized to weight loss, sodium restriction, or a control group.22 Post-trial follow-up examinations were conducted in 181 of the 208 participants studied.19 During the original 18-month study, significant weight loss was achieved in the group randomized to the weight loss intervention and was associated with a significant reduction in blood pressure. However, after 7 years of follow-up, the weight loss group did not differ in body weight or urinary sodium excretion from the other intervention groups. Despite this apparent loss of the intervention’s effects, the weight loss group had an incidence of hypertension that was reduced by 77%.

Phase 2 of the TOHP had a similar design but enrolled more patients and had 3 to 4 years of follow-up.19 The group randomized to weight loss (595 individuals who were at 110%–165% of ideal body weight, with high-normal blood pressure) had a 2-kg weight reduction at 3 years of follow-up when compared with the control group. This modest weight loss was associated with a risk ratio of 0.81 (19% risk reduction) for the development of hypertension; those with a sustained 4.5-kg weight loss had a risk ratio of 0.35 (65% risk reduction).

In a substudy of the Hypertension Optimal Treatment (HOT) study, obese hypertensive patients were randomly assigned to receive a weight loss intervention, including individual and group counseling, and were compared with individuals who received no intervention.20 Those in the weight loss group lost significantly more weight than the control group during the initial 6 months following randomization, but at 30 months of follow-up there was no significant difference between the groups. Yet, patients in the weight loss group used fewer medications to achieve the same level of blood pressure.

**DASH Diet and Reduced Sodium Intake**

Observational studies and clinical trials have shown that a vegetarian diet or one replacing animal products with vegetable products is associated with lower blood pressure.22,23 Such diets typically contain less fat, more fiber, and higher amounts of potassium, magnesium, and calcium than the typical U.S. diet. Increased intake of each of these nutrients is associated with lower blood pressure, but studies that have tested the nutrients individually have shown only modest effects on blood pressure.24-26 These findings led to the hypothesis that each nutrient by itself has a small effect and only when all are consumed together will there be a clinically significant effect.

**DASH trial.** The DASH trial27 was designed to study this hypothesis with the hope of identifying a dietary pattern that lowers blood pressure and is acceptable to the general population. In this trial, participants with prehypertension or stage 1 hypertension were randomized to 1 of 3 intervention diets for an 8-week period: (1) a control diet with the composition of a typical U.S. diet, (2) a diet enriched in fruits and vegetables (but otherwise similar to the control diet in fat and carbohydrate content), or
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(3) a diet containing increased fruits and vegetables, increased low-fat dairy products, and overall reduced total and saturated fat and cholesterol (DASH diet). All diets had similar sodium content (approximately 3 g/day). During the study, caloric intake was modified as necessary to prevent significant weight change, which might independently affect blood pressure.

The DASH diet had a significant effect on both systolic and diastolic blood pressures, and the fruits and vegetables diet produced an intermediate effect. The response was greater in African Americans than in whites, and hypertensive participants had a change in blood pressure (−11.6/−5.5 mm Hg) that rivaled the effects of antihypertensive medication. At the end of the study, 70% of hypertensive participants eating the DASH diet had normal blood pressure levels (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg) compared with only 23% of those eating the control diet. The DASH diet was well accepted, and compliance with the feeding protocol exceeded 90%.

**DASH-Sodium trial.** The DASH-Sodium trial added significant new information on the role of sodium restriction in lowering blood pressure. The DASH-Sodium trial was a similar feeding study that compared the effects on blood pressure of 3 levels of sodium intake in 2 dietary patterns: a control diet and the DASH diet. The 3 sodium levels were defined as “higher” (150 mmol/day, typical of U.S. consumption), “intermediate” (100 mmol/day, the upper limit of current U.S. recommendations), and “lower” (50 mmol/day, a possible optimal level). The DASH diet and sodium restriction significantly lowered blood pressure more than either intervention alone, and this effect was seen in all subgroups, including those with prehypertension.

The DASH eating plan would be appropriate to recommend to the case patient. Following this dietary plan requires attention to food groups, serving sizes, one’s caloric requirements, and food choices. The 8 to 10 servings of fruits and vegetables per day and 3 servings per day of dairy products are approximately twice the amount of these foods typically eaten per day by U.S. adults. The DASH eating plan can be modified so that daily sodium intake is 2400 or 1500 mg. Low sodium foods may be more difficult to identify. Also, while higher sodium intake is associated with increased risk of cardiovascular disease, particularly in obese individuals, there has been debate as to whether a very low sodium diet should be advocated for all, given the physiologic changes that accompany sodium restriction (e.g., increased plasma renin activity and angiotensin II levels, increased sympathetic nervous system activity and insulin resistance).

### Aerobic Exercise

Often promoted as a tool to facilitate weight loss, exercise also has independent favorable effects on blood pressure. Indeed, the combination of exercise and weight loss results in lower blood pressure than either intervention alone. With exercise, the mechanisms that mediate blood pressure lowering are not fully understood, but the effects appear to be independent of changes in weight or body composition.

Three meta-analyses have analyzed results from clinical trials assessing the blood pressure effects of walking, aerobic exercise, and resistance exercise. From these studies one may conclude that regular aerobic exercise produces the greatest blood pressure lowering (approximately −7/−6 mm Hg) when compared with walking (−3/−2 mm Hg) or resistance exercise (−3/−3 mm Hg). Thus, the optimal exercise program for blood pressure reduction should include moderate-intensity aerobic exercise 3 to 5 times per week for 30 to 60 minutes per session. Resistance training exercise has limited effects on blood pressure and should not be recommended as the sole form of exercise.

There is no apparent age- or sex-related differences in the response to exercise. Weight loss is facilitated by exercise programs that expend 300 to 500 kcal/day. Exercise intensity and duration should be appropriate to the individual’s abilities and concomitant medical conditions. In some cases, an assessment of cardiovascular risk (i.e., supervised exercise test) may be appropriate before participation in a regular exercise program.

### CASE 1 CONTINUED

The patient was referred to a dietitian for instruction in how to modify her diet according to the DASH eating plan. She also is encouraged to begin exercising again and is advised to aim for at least 30 minutes of brisk aerobic activity at least 3 or 4 days per week. The patient subsequently meets with the dietitian, who reviews the principles of the DASH eating plan and provides instruction in food selection and meal planning. She also purchases a treadmill, which she places in a prominent place in her home.

At a follow-up visit 3 months later, the patient expresses concern about being able to stick with the DASH diet because her family has not been supportive. However, she is proud of the fact that she has been using the treadmill 3 days each week. Her blood pressure is 148/82 mm Hg in the right arm while seated, and she has lost 3.6 kg (8 lb). The patient is encouraged to continue exercising. A follow-up visit is scheduled for 3 months later.
At the next visit, the patient’s blood pressure is 156/82 mm Hg in the right arm while seated, and she has regained 1.4 kg (3 lb). She admits that she is slipping back to her old eating habits, although she continues to use the treadmill 2 or 3 days each week. Further encouragement is offered, and she is strongly advised to return to the dietitian. At a follow-up visit 6 months later, her weight has returned to its original level, and her blood pressure is measured at 164/88 mm Hg.

- Is pharmacologic therapy indicated for this patient and, if so, what would be an appropriate first step?

Despite her best effort, this patient is struggling to adhere to lifestyle changes aimed at lowering her blood pressure. After a 6-month trial of nonpharmacologic therapy, her systolic blood pressure remains above the JNC 7 goal of less than 140 mm Hg. While it would be appropriate to seek ways to motivate the patient to successfully adopt healthy diet and exercise habits, it is important to recognize that pharmacologic therapy is likely needed to lower her blood pressure toward normal.

INITIAL PHARMACOLOGIC THERAPY

The JNC 7 outlined an approach to initiating pharmacologic therapy that recognizes both stage of hypertension and potential coexisting conditions (compelling indications). These recommendations are summarized in the Figure and briefly discussed below.

Uncomplicated Hypertension

Stage 1 hypertension. For many patients with stage 1 hypertension, risk of cardiovascular complications over a 5-year period is low and treatment goals may be achieved with a single antihypertensive agent. Based on the results of the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT), a thiazide-type diuretic is an appropriate first-line therapy for most patients without compelling indications. ALLHAT, the largest trial undertaken in patients with hypertension, compared the occurrence of major cardiovascular events in hypertensive patients receiving chlorthalidone, doxazosin, lisinopril, or amlodipine. The study showed a significant difference between the groups treated with chlorthalidone (a diuretic) and those receiving doxazosin (an α-blocker). Doxazosin was associated with significantly greater cardiovascular events and heart failure, which prompted early termination of this arm of the study. The other treatment arms continued until completion of the study, which showed no difference in CHD events between patients treated with lisinopril, amlodipine, or chlorthalidone. These data provide strong support for use of a low-dose diuretic-based regimen as first-line therapy in hypertensive subjects.

Stage 2 hypertension. When initial levels of blood pressure are at stage 2 hypertension, it is unlikely that control will be achieved with a single antihypertensive agent. Thus, it is recommended that most patients with stage 2 hypertension be started on treatment with 2 agents with different mechanisms of action. The goal of combination therapy is to maximize efficacy by employing agents with additive or synergistic effects on blood pressure while minimizing side effects. A diuretic should be one of the agents used, not only based on ALLHAT, but because diuretics have proven effectiveness in lowering blood pressure when used in multidrug combinations. The most frequently prescribed combinations include a low-dose thiazide diuretic together with a β-blocker, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin-receptor
blocker (ARB). Combinations of an ACE inhibitor and a calcium channel blocker also are available. All fixed-dose combinations have been shown to be more effective than either agent alone at similar doses. In some patients, the compliance gained with fixed-dose combination pills is worth the constraints on dosage selection.

**Patients with Compelling Indications**

Blood pressure lowering *per se* may not equally impact all complications of hypertension—a reflection of the complex mechanisms involved in the etiology of this disease. Specific drugs may offer advantages in certain patients and for certain types of outcomes. In particular, there are compelling indications for specific antihypertensive agents when patients have coexisting conditions, such as heart failure, diabetes mellitus, or chronic kidney disease (Table 2). Although diuretics have been shown effective in many of these circumstances, additional or alternative agents may be used and are supported by evidence from clinical trials. For example, patients with congestive heart failure and hypertension are likely to derive greater benefits from an ACE inhibitor than a calcium channel blocker. While both medications may equally lower blood pressure, there is a significant and favorable impact of ACE inhibitors on the pathophysiology of congestive heart failure.

**When Initial Therapy Fails**

In patients with stage 1 hypertension, if blood pressure is not well controlled with a single antihypertensive agent, there are 3 alternatives: up-titrate the dose, switch to an alternative monotherapy agent, or combine a second agent with the first. Up-titration of initial doses of antihypertensive medication may improve blood pressure control in some patients but also increases the risk of side effects. For patients who experience adverse effects or have no response to the initial drug selection, an alternative medication from a different class can be substituted. Replacing the ineffective medicine with another agent may ultimately benefit some patients but can be time-consuming for those who do not respond. There are several reasons to consider combination drug therapy, employing smaller doses of 2 drugs with different mechanisms of action to maximize efficacy while minimizing side effects. If a diuretic was not chosen as the initial drug, it is appropriate to add one as a second agent because of the ability of diuretics to enhance the blood pressure-lowering effects of most classes of antihypertensive drugs.

**CASE CONCLUSION**

The endocrinologist recommends that the patient start hydrochlorothiazide 25 mg/day with the goal of lowering her systolic blood pressure below 140 mm Hg. She encourages the patient to redouble her efforts to eat a healthier diet, perhaps by making meal planning and preparation more of a family affair.

The patient returns 1 month later. Her blood pressure is now 142/78 mm Hg, and she has lost 1.1 kg (2.5 lb). Although she is still struggling to adhere to the DASH diet and to exercise regularly, she has convinced her daughter to also use the treadmill and to help with meal preparation. She is scheduled to return to her primary care provider for a reevaluation in 3 months.

**CHALLENGES IN TREATING HYPERTENSION**

**CASE PRESENTATION**

A 60-year-old man is referred to an endocrinologist for evaluation of hypertension that is difficult to control.

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**Table 2. Compelling Indications for Individual Drug Classes**

<table>
<thead>
<tr>
<th>Compelling Indications</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
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<tr>
<td>Post–myocardial infarction</td>
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<td>•</td>
<td>•</td>
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<td></td>
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<tr>
<td>High coronary disease risk</td>
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<td></td>
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<tr>
<td>Diabetes</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
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<tr>
<td>Chronic kidney disease</td>
<td>•</td>
<td>•</td>
<td></td>
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<td></td>
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<tr>
<td>Recurrent stroke prevention</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AA = aldosterone antagonist; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BB = β-blocker; CCB = calcium channel blocker. (Adapted from Chobanian et al.)
**History**

The patient recalls being told he had high blood pressure about 20 years ago, for which he was intermittently treated until about 8 years ago. At that time, he began seeing an internist for regular follow-up subsequent to a diagnosis of renal calculi. The internist initiated antihypertensive therapy with diltiazem, which did not control the patient’s blood pressure. The physician subsequently changed his treatment to a combination of irbesartan, hydrochlorothiazide, and amlodipine. The patient’s home blood pressure readings while on the combination regimen have been less than 130/80 mm Hg. However, over the past 6 months, the patient has twice gone to the emergency department complaining of headaches and “heart pounding” associated with blood pressure levels of 180/100 mm Hg. These events occurred soon after he had an angry discussion with his daughter. A recent echocardiogram showed normal function and no left ventricular hypertrophy.

**Physical Examination**

The patient is 178 cm (70”) in height and weighs 84.1 kg (185 lb), with a BMI of 26.6 kg/m². Blood pressure is 156/94 mm Hg in the right arm while seated, and pulse is 84 bpm. Ocular examination reveals no retinopathy. The heart and vascular examination is normal. The abdominal examination reveals no masses, striae, organomegaly, or bruits. There is no peripheral edema.

**Laboratory Examination**

Laboratory studies performed a few days earlier revealed normal electrolytes, tests of liver and kidney function, and complete blood count. In addition, fasting blood glucose and lipid levels were all within normal limits: blood glucose concentration, 84 mg/dL; total cholesterol, 182 mg/dL; triglycerides, 78 mg/dL; LDL, 122 mg/dL; and HDL, 47 mg/dL. Urinary albumin level was 14 mg/g creatinine.

- **What are possible explanations for this patient’s recent high blood pressure readings?**

**RESISTANT HYPERTENSION**

This patient presents with a recent worsening of his blood pressure despite continued treatment with a regimen that was previously effective. Some patients may have difficult-to-control blood pressure, manifesting as failure to achieve target blood pressure levels or loss of control despite continued use of multiple medications. Failure to achieve target levels of blood pressure despite use of 3 antihypertensive agents warrants consideration of possible contributors to resistant hypertension (Table 3). Several environmental factors and concomitant medical conditions or their treatments may affect blood pressure and its response to antihypertensive medications. However, 4 major factors—white coat hypertension; secondary causes, patient factors (eg, adherence), and clinician factors—should be considered in the evaluation of patients whose blood pressure response to a reasonable antihypertensive regimen is inadequate.

**White Coat Hypertension**

Blood pressure measured in the office setting may not reflect the patient’s overall blood pressure load. However, office-measured blood pressure remains a relevant parameter on which to base treatment decisions, because the evidence associating hypertension with cardiovascular disease stems from such measurements. Out-of-clinic blood pressure measurements will invariably be lower in almost all individuals, but in some patients this difference may be marked. Scenarios suggesting white coat hypertension include: (1) a patient with apparent drug resistance, (2) a patient who develops hypotensive symptoms

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### Table 3. Causes of Resistant Hypertension

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improper blood pressure measurement</td>
</tr>
<tr>
<td>Volume overload and pseudotolerance</td>
</tr>
<tr>
<td>Excess sodium intake</td>
</tr>
<tr>
<td>Volume retention from kidney disease</td>
</tr>
<tr>
<td>Inadequate diuretic therapy</td>
</tr>
<tr>
<td>Drug-induced or other causes</td>
</tr>
<tr>
<td>Nonadherence</td>
</tr>
<tr>
<td>Inadequate doses</td>
</tr>
<tr>
<td>Inappropriate combinations</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs; cyclooxygenase-2 inhibitors</td>
</tr>
<tr>
<td>Cocaine, amphetamines, other illicit drugs</td>
</tr>
<tr>
<td>Sympathomimetics (decongestants, anorectics)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Adrenal steroids</td>
</tr>
<tr>
<td>Cyclosporine and tacrolimus</td>
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<tr>
<td>Erythropoietin</td>
</tr>
<tr>
<td>Licorice (including some chewing tobacco)</td>
</tr>
<tr>
<td>Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange)</td>
</tr>
</tbody>
</table>

**Associated conditions**

- Obesity
- Excess alcohol intake

Adapted from Chobanian et al.²
Primary aldosteronism is the ratio of plasma aldosterone to plasma renin activity. Levels greater than 30 suggest primary aldosteronism. Secondary Causes

Endocrinologists may be asked to assist in evaluating patients for the presence of the following endocrine disorders that may be associated with hypertension.

Primary aldosteronism. Primary aldosteronism is emerging as a frequent abnormality in patients with hypertension, possibly as a result of better detection methods. Although patients with resistant hypertension and hypokalemia have hallmarks of hyperaldosteronism and therefore draw attention to this process as a diagnostic possibility, many patients with documented aldosteronism have neither of these abnormalities. The most widely recommended screening test for aldosteronism is the ratio of plasma aldosterone to plasma renin activity. Levels greater than 30 suggest primary aldosterone excess; higher levels increase the likelihood further still. It is important to note that comitant medications may alter the ratio, clouding the interpretation of whether aldosterone excess is indeed present. For example, β-blockers reduce plasma renin activity, making a higher ratio more likely even in the presence of normal aldosterone levels. Diuretics, ACE inhibitors, or ARBs may increase renin and therefore make a lower ratio possible.

Renal artery stenosis. Renal artery stenosis with accompanying renovascular hypertension may be a cause of refractory hypertension. Younger individuals may present with a syndrome of fibromuscular dysplasia of mid-distal renal arteries, whereas older patients who are at risk for atherosclerotic disease may develop stenotic lesions at the ostia of the renal arteries. Magnetic resonance angiography is now the preferred screening test for the presence of renal artery stenosis. This test defines the likely anatomic basis for renovascular hypertension. Magnetic resonance angiography is semi-quantitative in its assessment of renal artery stenosis, but it also provides information of hemodynamic significance by evaluating renal artery flow and kidney size and assessing for the presence of poststenotic dilatation.

Pheochromocytoma. Pheochromocytoma is a rare cause of resistant hypertension. While classic signs and symptoms of catecholamine excess (eg, sweating, palpitations, headache, paroxysmal severe hypertension) may be present, patients may not present with all of these features. The case patient has some of these features and may be considered for evaluation of pheochromocytoma. Some patients may come to attention when a familial syndrome, such as multiple endocrine neoplasia type 2, is being considered; other patients may be identified when an incidentally discovered adrenal mass is evaluated for hormonal excess. Measurement of plasma metanephrine is the preferred screening test for pheochromocytoma. This test may be readily obtained in the ambulatory care setting and does not require urine collections. Radiographic localization of pheochromocytoma typically is possible using abdominal computed tomography or magnetic resonance imaging, as more than 90% of tumors reside within the abdomen. Occasionally, extra-adrenal or metastatic tumors require additional localization techniques, such as 123I-metaiodobenzylguanidine or 111In-octreotide scintigraphy.

Patient Factors

Patient-related factors that may impact adherence with medication regimens include: (1) access to care, (2) trust in one’s care provider(s), (3) lack of health information related to the goals of treatment, (4) fear of side effects, and (5) cost of medications. Each of these factors should be considered in determining whether adherence is an issue for a patient.

Many patients fail to refill prescriptions regularly enough to maintain a supply of pills. For antihypertensive medications, this lack of adherence over a 4-year period ranges from 50% to 80%, in part related to the type of medication used. Issues such as cost, the presence of concomitant medical conditions that independently require other medications, and the complexity of the medication regimen each may play a role. For example, patients who are prescribed many drugs that must be taken at different times of the day may find it difficult to remember to take the medications as prescribed or may find the complex regimen too onerous.
Clinician Factors

Clinicians, by their lack of response to the patient with elevated blood pressure, may contribute to the problem of refractory hypertension. The term clinical inertia has been used to describe the not uncommon scenario in which patients with documented elevated blood pressure leave the clinic without action taken. In a study of patients with documented high blood pressure who were cared for in an integrated delivery system, nearly two thirds of the patients did not have action taken to address their hypertension. The issues involved are complex, reflecting the multifaceted relationship between clinical providers and their patients. Lack of knowledge about appropriate blood pressure targets or access to medication seems not to be involved. A systems approach to treatment and/or more frequent use of treatment algorithms based on blood pressure measurements (as used in clinical trials) may help remove this barrier to treatment.

**CASE 2 CONCLUSION**

The patient is evaluated for pheochromocytoma given his apparent worsening of blood pressure accompanied by symptoms of catecholamine excess (ie, palpitations, headache). Plasma metanephrine level is normal. Further questioning reveals that the patient has become greatly concerned about his adult daughter’s welfare; he has had many contentious discussions with her, which twice sparked symptoms that led to his recent emergency department visits. There is a high suspicion that his blood pressure is not consistently elevated based on his home readings and the absence of target organ damage.

The patient completes a 24-hour ambulatory blood pressure test. The results show an average blood pressure of 118/76 mm Hg. The patient is reassured that his blood pressure is adequately controlled and encouraged to seek counseling for the strain in his family relationships.

**REFERENCES**


