CLINICAL PRACTICE

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Initial Treatment of Hypertension

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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A 56-year-old woman presents for elevated blood pressure, which was noted at a job-site screening. She has gained 20 lb (9.1 kg) during the past 5 years and takes naproxen sodium (at a dose of 220 mg daily) for joint pain. She has never smoked, and she consumes one or two alcoholic drinks daily. Both of her parents received a diagnosis of hypertension in their 50s. On examination, the blood pressure is 162/94 mm Hg in both arms while the patient is seated and 150/96 mm Hg while the patient is standing. The body-mass index (the weight in kilograms divided by the square of the height in meters) is 29. Her examination is notable only for abdominal obesity without bruits or masses. The serum level of sodium is 138 mmol per liter, potassium 3.8 mmol per liter, calcium 9.4 mg per deciliter (2.35 mmol per liter), fasting glucose 105 mg per deciliter (5.8 mmol per liter), and creatinine 0.8 mg per deciliter (71 μmol per liter). Urinalysis is negative. How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

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Hypertension, the elevation of systolic blood pressure, diastolic blood pressure, or both above normal levels, is common in developed and developing countries and increases in prevalence with age. The threshold blood pressure for the diagnosis has declined over time on the basis of trials showing benefits of treatment to incrementally lower blood-pressure targets in reducing mortality and cardiovascular-event rates.[1] Although in recent years hypertension has been defined as a blood pressure of 140/90 mm Hg or more, the 2017 American College of Cardiology–American Heart Association (ACC–AHA) Hypertension Guideline adopted a lower threshold, in which hypertension is defined as a systolic blood pressure of 130 mm Hg or more or a diastolic blood pressure of 80 mm Hg or more (Table 1).[2] Among adults in the United States, the overall prevalence of hypertension was 31.9% under the previous definition (blood pressure, ≥140/90 mm Hg) and is 45.6% according to the 2017 ACC–AHA guideline definition (blood pressure, ≥130/80 mm Hg).[3] Similarly, the rate of hypertension control was 61.0% among those receiving treatment at a target of less than 140/90 mm Hg but only 46.6% at a target of less than 130/80 mm Hg.[3]

Hypertension is a leading risk factor for death and disability, including stroke, accelerated coronary and systemic atherosclerosis, heart failure, chronic kidney disease, and death from cardiovascular causes (Fig. 1). From 1990 through 2015, the estimated global annual rate of death associated with a systolic blood pressure of 140 mm Hg or more increased from 97.9 to 106.3 per 100,000 persons, where-

KEY CLINICAL POINTS

INITIAL TREATMENT OF HYPERTENSION

- The 2017 ACC–AHA Hypertension Guideline redefines hypertension as a systolic blood pressure of 130 mm Hg or more or a diastolic blood pressure of 80 mm Hg or more and lowers the blood-pressure target to less than 130/80 mm Hg.
- This blood-pressure target is supported by the SPRINT trial, which showed lower hypertension-associated morbidity and all-cause mortality with a systolic blood-pressure target of less than 120 mm Hg than with a target of less than 140 mm Hg; electrolyte abnormalities, syncope, and acute kidney injury were more common in the lower-target group.
- The initial assessment should consider coexisting conditions, including cardiovascular disease, diabetes mellitus, chronic kidney disease, and elevated risk of cardiovascular disease, in determining when to start blood-pressure–lowering medication.
- Recommended lifestyle modifications include restriction of dietary sodium intake, weight loss if the patient is overweight, exercise, moderation of alcohol intake, and increased consumption of potassium-rich foods.
- The initial antihypertensive agent should generally be selected from one of four drug classes shown to reduce cardiovascular events: ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and thiazide-type diuretics.
- Repeat visits are required to ensure ongoing hypertension control.

Table 1. Classification of Blood Pressure in Adults.*

Blood-Pressure Category	Definition
Normal	Systolic pressure of <120 mm Hg and diastolic pressure of <80 mm Hg
Elevated	Systolic pressure of 120–129 mm Hg and diastolic pressure of <80 mm Hg
Hypertension	
Stage 1	Systolic pressure of 130–139 mm Hg or diastolic pressure of 80–89 mm Hg
Stage 2	Systolic pressure of ≥140 mm Hg or diastolic pressure of ≥90 mm Hg

* Definitions are derived from the 2017 American College of Cardiology–American Heart Association Hypertension Guideline.[2] Persons with systolic blood pressure and diastolic blood pressure in different categories should be designated in the higher blood-pressure category. Diagnosis is based on the average of two or more readings taken on two or more occasions.

as the number of disability-adjusted life-years increased from 5.2 million to 7.8 million.[4]

Lifestyle factors that are associated with an increased risk of hypertension and greater severity include high sodium intake,[5] weight gain and obesity,[6] excess alcohol intake,[7] and the use of certain medications, particularly nonsteroidal antiinflammatory drugs (NSAIDs), stimulants, and decongestants. There is often a genetic predisposition that is probably polygenic for most persons. Hypertension that manifests during pregnancy as preeclampsia or gestational hypertension is associated with an increased likelihood of future sustained hypertension and cardiovascular events.[8]

STRATEGIES AND EVIDENCE

EVALUATION

The first step is to confirm the diagnosis of hypertension. Guidelines recommend at least two blood-pressure measurements on at least two occasions with the use of a standardized measurement technique and validated equipment, including a cuff of correct size.[2] Measurements should be made with the back supported, legs uncrossed, feet on the floor, and the measurement arm supported on a table at heart level after the patient has sat quietly for 5 minutes.

Current methods rely on aneroid sphygmomanometers or oscillometric devices in which

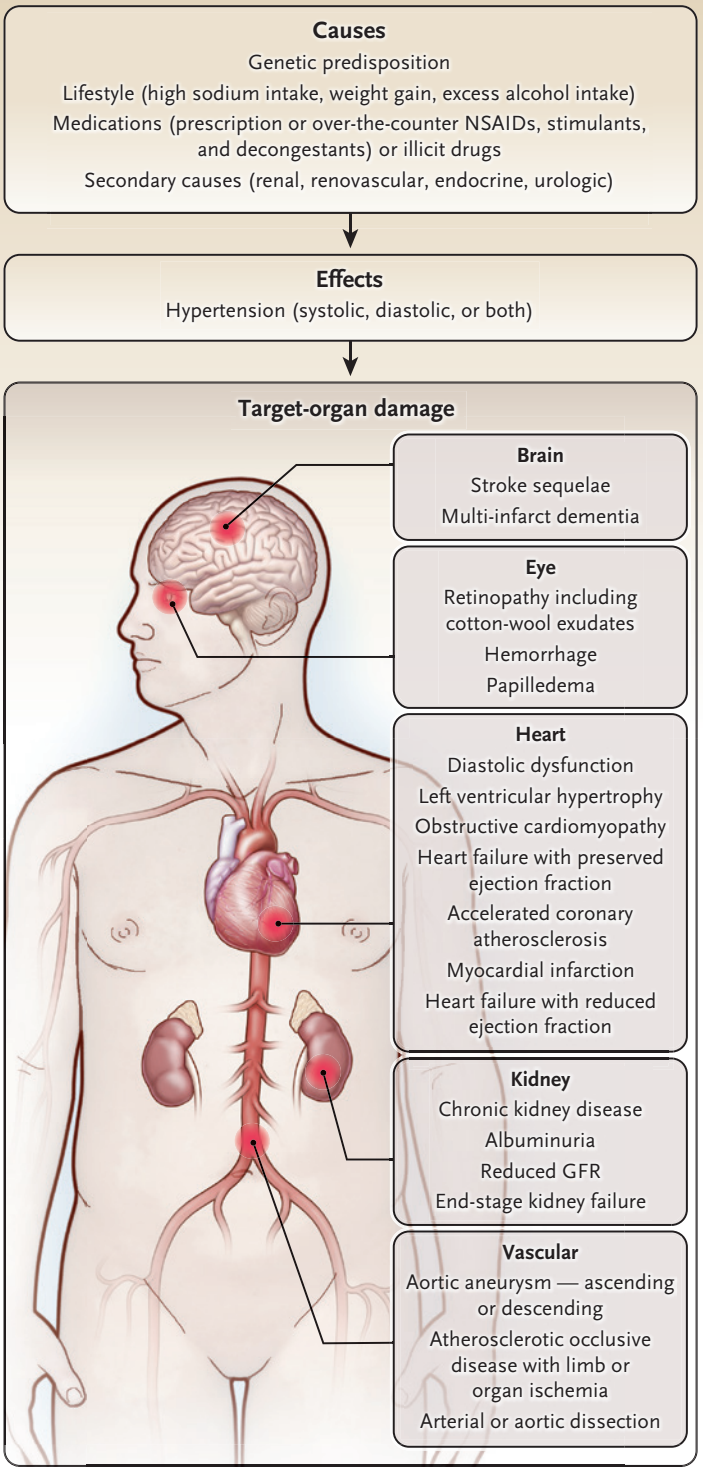

Figure 1. Pathophysiology of Hypertension.

GFR denotes glomerular filtration rate, and NSAIDs nonsteroidal antiinflammatory drugs.

blood pressure is calculated from maximal oscillations of the blood-vessel wall during cuff deflation (defined as mean arterial pressure), with systolic and diastolic pressures calculated with the use of proprietary algorithms.[9] Automated devices that take two to six serial measurements and determine the mean are increasingly used in outpatient clinics, and the readings correlate closely with those of ambulatory blood-pressure monitoring while the patient is awake.[10] These devices allow an attendant to place the cuff and leave the room, minimizing the "white coat" effect (i.e., blood pressure elevated in the office but normal outside).

Masked hypertension should be considered when office blood pressures are controlled but the patient has elevated home measurements or a greater severity of hypertension-associated target-organ damage than expected. Ambulatory blood-pressure monitoring is useful in assessing these possibilities; if such monitoring is unavailable or for measurements obtained over several days, home blood-pressure monitoring is an alternative.[11]

Once the diagnosis is confirmed, a careful history taking should assess coexisting conditions and contributing factors, including lifestyle practices, other cardiovascular risk factors that are associated with hypertension, and features to suggest a secondary cause of hypertension. A gradual rise in blood pressure that is associated with weight gain, in combination with a positive family history, supports primary hypertension, whereas severe or resistant hypertension, accelerated target-organ damage, or other symptoms or signs suggest a secondary cause that merits further testing and referral (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The physical examination should include cardiac and vascular evaluation and assessment of target-organ damage (Fig. 1). A thigh blood-pressure measurement is recommended for adults younger than 30 years of age to exclude aortic coarctation, and blood-pressure measurement while the patient is standing is recommended for older adults to assess orthostatic blood-pressure changes.

Initial laboratory testing should assess for coexisting conditions that may affect the patient's response to medication and assess for target-organ damage. Such testing includes assessment

of serum levels of sodium, potassium, calcium, uric acid, creatinine (with estimated glomerular filtration rate), hemoglobin, and thyrotropin; a lipid profile; urinalysis; and electrocardiography. Patients with diabetes mellitus or chronic kidney disease should have the urinary albumin-to-creatinine ratio checked initially and annually.

MANAGEMENT

Treatment of hypertension includes nonpharmacologic and pharmacologic approaches. Treatment decisions depend on whether there is preexisting cardiovascular disease, diabetes mellitus, or chronic kidney disease. For patients with stage 1 hypertension and without these conditions, the 2017 ACC–AHA guideline recommends calculation of the estimated 10-year risk of cardiovascular disease (http://tools.acc.org/ASCVD-Risk-Estimator/).[2] If this risk is less than 10%, it is reasonable to implement lifestyle modifications alone for a period of 3 to 6 months. For those with stage 2 hypertension or with preexisting cardiovascular disease, diabetes mellitus, chronic kidney disease, or a 10-year risk of cardiovascular disease of 10% or higher, both lifestyle change and medication are recommended. For all patients with hypertension, a blood-pressure target of less than 130/80 mm Hg is advised.

Lifestyle Changes

Recommended strategies include restriction of dietary sodium intake below 1500 mg per day,[12,13] weight loss if the patient is overweight or obese,[14] aerobic or resistance exercise for 90 to 150 minutes per week,[15,16] moderation of alcohol intake (≤2 drinks daily for men and ≤1 drink for women),[17,18] and enhanced intake of potassium-rich foods.[19] Each of these strategies is likely to reduce systolic pressure by 3 to 8 mm Hg and diastolic pressure by 1 to 4 mm Hg.[20] The Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes the consumption of fresh produce, whole grains, and low-fat dairy products and which limits sodium intake, was associated with a reduction of 11.4/5.5 mm Hg in blood pressure, as compared with a control diet.[21] Patients should be encouraged to minimize the use of NSAIDs, decongestants, and amphetamines (as used for attention deficit–hyperactivity disorder). Other behaviors that are associated with cardiovascular risk, including tobacco use and a sedentary lifestyle, should also be addressed.

Evidence Supporting Pharmacologic Therapy

Multiple clinical trials — including (but not limited to) the Veterans Administration Cooperative Study[22,23] (focusing on diastolic hypertension), the Systolic Hypertension in the Elderly Program trial,[24] and the Systolic Hypertension in Europe trial[25] — have shown that blood pressure can be effectively reduced by medications and that doing so results in a reduced incidence of target-organ events.

Other trials have compared first-line therapies with the use of different drug classes.[26,27] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) randomly assigned more than 40,000 patients at high cardiovascular risk to initial therapy with chlorthalidone, amlodipine, lisinopril, or doxazosin and allowed additional medications to achieve a blood pressure of less than 140/90 mm Hg.[27] The doxazosin group was stopped early owing to a higher incidence of heart failure. Chlorthalidone-based therapy resulted in lower blood-pressure levels than the other agents, fewer heart-failure events than amlodipine, and fewer combined cardiovascular events, strokes, and heart-failure events than lisinopril.

More recently, the Systolic Blood Pressure Intervention Trial (SPRINT) randomly assigned 9361 persons with a systolic blood pressure of 130 to 180 mm Hg and high cardiovascular risk to a systolic blood-pressure target of either less than 120 mm Hg or less than 140 mm Hg.[28] The trial was stopped early after 3.3 years for demonstrated benefit of the lower blood-pressure target with respect to the primary composite outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) (hazard ratio, 0.75; 95% confidence interval [CI], 0.64 to 0.89) and all-cause mortality (hazard ratio, 0.73; 95% CI, 0.60 to 0.90). Patients in the intensive-treatment group required an average of one additional medication (2.8 drugs, as compared with 1.8 for standard treatment).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, with a trial design nearly identical to that of SPRINT but involving

4733 participants with type 2 diabetes, showed no significant benefit for the lower blood-pressure target with respect to the primary outcome, although there was a significant difference in the incidence of stroke that favored the lower target.[29] A possible contributor to the negative results of the ACCORD trial was the power of the trial, with fewer events than predicted in the group with a higher blood-pressure target.

Drug Selection

The initial agent can be selected from one of four drug classes: angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium-channel blockers, and thiazide-type diuretics; each class has been shown to reduce cardiovascular events (Table 2).[27] The patient's lifestyle, coexisting conditions, and clinical characteristics should be considered in selecting an agent. For example, patients with a high salt intake (e.g., eating primarily processed foods) may have a greater blood-pressure reduction with diuretic therapy, whereas those restricting salt intake may have a greater response to blockade of the renin–angiotensin system. This approach has been extended by some providers to use the patient's age and race as predictors of blood-pressure response[30] and by others to use renin profiling for drug selection,[31] although data are not conclusive.

Caution is advised with thiazide use in patients 65 years of age or older, particularly in women[32] and in patients of either sex who have hyponatremia or a low normal sodium level at baseline; in such patients, the serum level of sodium should be checked within 1 to 2 weeks after a thiazide diuretic has been started or the dose has been increased. If hyponatremia develops, an agent from a different class can be selected. If a diuretic is needed later, a long-acting loop diuretic can be used.

ACE inhibitors are effective and have an acceptable side-effect profile in most patients, although cough develops in up to 20% of patients.[33] Angioedema is an infrequent complication overall but is two to four times as common among blacks as among whites (estimated incidence, 3.9 cases per 1000 person-years among blacks and 0.8 cases among whites).[34] If angioedema occurs, an ARB can usually be substituted. Thiazide-type diuretics or calcium-channel blockers were more effective than ACE inhibitors as first-line agents for black patients with hypertension in ALLHAT.[27] However, calcium-channel blockers are associated with additional side effects, primarily edema for the dihydropyridine agents (nifedipine, amlodipine, and others) and constipation for the nondihydropyridines (verapamil and diltiazem). In most cases, these agents are better used for add-on therapy if blood pressure remains uncontrolled. (Table S2 in the Supplementary Appendix provides information on other agents that may be used for blood-pressure control.)

Patients with certain coexisting conditions may benefit from specific agents (Table 2, and Table S2 in the Supplementary Appendix). For example, sustained-release beta-blockers are indicated in patients with congestive heart failure, after myocardial infarction, for arrhythmias, and for migraine prophylaxis and will also treat the patient's hypertension. An ACE inhibitor or ARB should be prescribed for most patients with chronic kidney disease with albuminuria, with referral to a nephrologist for advanced chronic kidney disease (stage 3b or higher).

If the first agent that is selected has unacceptable side effects, it should be discontinued and an agent from a different drug class should be started. If the selected agent has an acceptable side-effect profile but is not effective, the dose may be increased or a second agent with a complementary mechanism of action can be added. In a recent meta-analysis, dual therapy involving at least one agent at a low dose had similar efficacy to that of higher-dose monotherapy but had fewer adverse effects.[35] The use of combination agents can reduce pill burden and shorten the time needed to reach blood-pressure goals; however, it may be prudent to use combination agents only after one component has been shown to have an acceptable side-effect profile in the patient, because an adverse reaction would potentially remove both agents as treatment options.

Additional Considerations

The need to take daily medications for a condition that is usually asymptomatic is challenging for many patients, particularly if they have adverse effects associated with a medication. A recent SPRINT substudy showed no significant differences between the intensive-therapy and standard-therapy groups in quality-of-life measures.[36] Electronic-monitoring data indicate that

Table 2. Initial Choices for Antihypertensive Agents and Usual Doses.*

Drug Class and Primary Agents	Usual Dose	Indications	Cautions and Side Effects
Thiazide-type diuretics			
Chlorthalidone	12.5–25 mg once daily	First-line therapy or add-on as second or third agent	Hyponatremia (more likely in older women), hypokalemia, orthostatic hypotension, hypovolemia
Hydrochlorothiazide	12.5–50 mg once daily		
Indapamide	1.25–2.5 mg once daily		
ACE inhibitors			
Benazepril	5–80 mg/day, in one or two doses	First-line therapy or add-on as second or third agent; CKD with albuminuria; congestive heart failure; after myocardial infarction	Do not use in combination with ARB or direct renin inhibitor; hyperkalemia; may cause serum creatinine elevation in patients with CKD or bilateral renal-artery stenosis; angioedema is infrequent but is 2 to 4 times as common among blacks as among whites; contraindicated in pregnancy
Fosinopril	10–80 mg/day, in one or two doses		
Lisinopril	5–40 mg once daily		
Moexipril	7.5–30 mg/day, in one or two doses		
Perindopril	4–16 mg/day, in one or two doses		
Quinapril	10–80 mg/day, in one or two doses		
Ramipril	2.5–20 mg/day, in one or two doses		
Trandolapril	2–8 mg/day, in one or two doses		
ARBs			
Azilsartan	40–80 mg once daily	First-line therapy or add-on as second or third agent; CKD with albuminuria; congestive heart failure; after myocardial infarction; alternative for patients with chronic cough or ACE-inhibitor–associated cough	Do not use in combination with ACE inhibitor or direct renin inhibitor; hyperkalemia; may cause serum creatinine elevation in patients with CKD or bilateral renal-artery stenosis; contraindicated in pregnancy
Candesartan	8–32 mg/day, in one or two doses		
Eprosartan	600 mg/day, in one or two doses		
Irbesartan	150–300 mg once daily		
Losartan	25–100 mg/day, in one or two doses		
Olmesartan	20–40 mg once daily		
Telmisartan	20–80 mg once daily		
Valsartan	80–320 mg once daily		
Calcium-channel blockers			
Dihydropyridine type			
Amlodipine	2.5–10 mg once daily	First-line therapy or add-on as second or third agent; no effect on serum creatinine level; minimal effect on cardiac output	Edema of the legs and feet; may worsen proteinuria; may worsen left ventricular outflow tract obstruction
Felodipine	2.5–10 mg once daily		
Isradipine	5–10 mg/day, in two doses		
Nicardipine ER	5–20 mg once daily		
Nifedipine ER	30–120 mg/day, in one or two doses		
Nisoldipine ER	17–34 mg once daily		
Nisoldipine ER, core coated	20–60 mg once daily		
Nondihydropyridine type			
Diltiazem SR	180–360 mg/day, in two doses	Tachycardia, left ventricular outflow tract obstruction, hyperdynamic cardiac function, migraine prophylaxis	Constipation; heart block if used in combination with beta-blocker
Diltiazem ER	120–480 mg once daily		
Verapamil SR	120–480 mg/day, in one or two doses		
Verapamil delayed-onset ER	100–480 mg once daily		

* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CKD chronic kidney disease, ER extended release, and SR sustained release.

adherence rates decline as the number of medications and overall pill burden rises: 79% for one daily dose, 69% for two doses, 65% for three doses, and 51% for four doses.[37] Nonpharmacologic therapy requires a strong ongoing commitment to be effective. Ultimately, the best strategies combine lifestyle efforts with medical therapies to achieve greater effect with the use of fewer medications and lower doses. Dose adjustment is recommended until blood-pressure goals are achieved, with interval laboratory testing to monitor for electrolyte disturbances or decline in renal function. Home blood-pressure measurements should be encouraged, although data are lacking to show that they improve blood-pressure control.[38,39] Home monitors should be checked annually for accuracy, and the technique for their use should be reviewed regularly. Inclusion of a nurse or pharmacist in the care team may facilitate more timely addition of new agents or adjustment of the dose when indicated.

AREAS OF UNCERTAINTY

There is continued debate regarding preferred blood-pressure targets and the benefits and risks of lower targets. In SPRINT, it was necessary to treat 61 patients at the lower systolic target of less than 120 mm Hg (vs. 140 mm Hg) to prevent one additional cardiovascular event and to treat 90 patients to prevent one additional death over a period of 3.26 years. Such estimates will vary with the absolute individual level of cardiovascular risk. Attendant costs of tight blood-pressure control warrant consideration, including higher rates of serious adverse events (hypotension, electrolyte abnormalities, syncope, and acute kidney injury) with intensive treatment than with standard treatment in SPRINT and additional pill burden. There is particular concern about harms of tight control in elderly persons, although a SPRINT substudy[40] involving patients 75 years of age or older showed significant benefit with the systolic blood-pressure target of less than 120 mm Hg, with absolute rates of and relative risks of hypotension, syncope, and electrolyte abnormalities that were similar to those in the overall SPRINT population; this substudy extended the benefits seen in an earlier trial involving elderly persons with a systolic blood-pressure target of less than 150 mm Hg.[41] Failure to measure blood pressure correctly may produce higher office readings and limit achievement of blood-pressure targets.

In addition, evidence is lacking to show that tight control prevents the progression of chronic kidney disease. Studies of blockers of the renin–angiotensin system have shown slowing of diabetic nephropathy,[42-44] yet such agents have not slowed the progression of chronic kidney disease in patients without albuminuria,[45-47] a finding that suggests the need for new approaches for this patient population.

GUIDELINES

In 2013, the National Heart, Lung, and Blood Institute transferred the development of hypertension guidelines to the ACC and the AHA. The 2017 ACC–AHA guideline replaces the 2014 guideline of the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[48] which was completed before the publication of SPRINT. (Blood-pressure targets of these and other guidelines are summarized in Table S3 in the Supplementary Appendix.) Recommendations in the present article are generally concordant with the 2017 ACC–AHA guideline.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette probably has primary hypertension, with a positive family history and contributing lifestyle factors, including weight gain and NSAID use. Her alcohol intake, at more than one drink per day, may be a contributor. I would initiate single-agent therapy for her stage 2 hypertension and encourage lifestyle changes, including sodium restriction, weight reduction, and discontinuation of contributing medications; attention to the lipid profile and glucose level is also warranted. A thiazide-type diuretic or ACE inhibitor is a reasonable first agent to prescribe, with follow-up blood-pressure and electrolyte measurements in 3 to 4 weeks. Dose increases and additional medications may be needed. I would recommend regular visits during dose adjustment, combined with home blood-pressure measure-

ments; lifestyle factors and medication adherence should be assessed at each visit. Once her blood pressure is at goal (<130/80 mm Hg), I would recommend follow-up at 6-month intervals.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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