

## CLINICAL PRACTICE

## Isolated Systolic Hypertension in the Elderly

Aram V. Chobanian, M.D.

*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.*

**A 68-year-old accountant visits his physician. He was told a year earlier that his blood pressure was somewhat elevated and was advised to reduce salt intake and increase physical activity. Otherwise he has been in good health and has no history or signs of cardiovascular or renal disease. On physical examination, his blood pressure is 178/72 mm Hg, with no clinically significant differences between arms or on standing. He has a body-mass index (the weight in kilograms divided by the square of the height in meters) of 28.4. The examination is otherwise unremarkable. Urinalysis is normal. The nonfasting blood glucose level is 98 mg per deciliter (5.4 mmol per liter), serum potassium 4.2 mmol per liter, and creatinine 1.2 mg per deciliter (106  $\mu$ mol per liter). How should he be further evaluated and treated?**

## THE CLINICAL PROBLEM

Hypertension is defined as a systolic pressure of 140 mm Hg or greater or a diastolic pressure of 90 mm Hg or greater.<sup>1</sup> Without treatment, approximately 30% of people over the age of 20 years in the United States have hypertension.<sup>2</sup> The prevalence increases markedly with age, such that approximately two thirds of those over 60 years of age have hypertension.<sup>3</sup> In the Framingham Heart Study, hypertension eventually developed in more than 90% of the participants who had had normal blood pressure at the age of 55 years.<sup>4</sup>

The pattern of blood-pressure elevation in the U.S. population also changes with age (Fig. 1).<sup>3</sup> Before reaching 50 years of age, most people with hypertension have elevated diastolic pressure.<sup>5</sup> After the age of 50 years, as systolic pressure continues to rise and diastolic pressure tends to fall, isolated systolic hypertension predominates (Fig. 2).

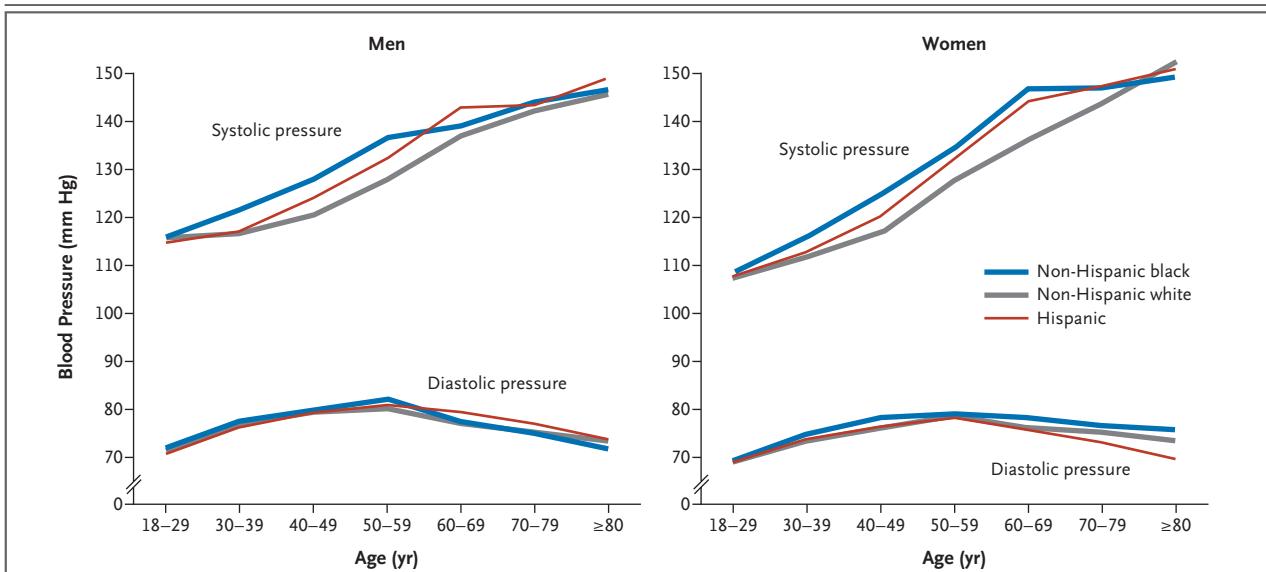
The risk of cardiovascular disease increases progressively and continuously with increases in systolic or diastolic blood pressure, approximately doubling for every 20/10 mm Hg incremental increase in blood pressure that occurs within the range of 115/75 to 185/115 mm Hg.<sup>6</sup> This increase in risk occurs independently of other risk factors for cardiovascular disease, which frequently cluster with hypertension and compound the risk.<sup>7</sup> Elevated systolic blood pressure is more important than elevated diastolic pressure as a risk factor for both cardiovascular and renal disease.<sup>8</sup>

Isolated systolic hypertension may occur in conditions associated with elevated cardiac output, such as anemia, hyperthyroidism, aortic insufficiency, arteriovenous fistula, and Paget's disease of bone.<sup>9</sup> However, most cases are caused by reduced elasticity and compliance of large arteries resulting from age and from the atherosclerosis-associated accumulation of arterial calcium and collagen and the degradation of arterial elastin. Stiffened conduit arteries cause an increase in the rate of return of reflected arterial pressure waves from the periphery, thereby raising the peak systolic pressure.<sup>10</sup> The blood-pressure elevation itself can promote further

From the Department of Medicine, Boston University Medical Center, Boston. Address reprint requests to Dr. Chobanian at the Department of Medicine, Boston University Medical Center, 650 Albany St., Boston, MA 02118, or at achob@bu.edu.

N Engl J Med 2007;357:789-96.

Copyright © 2007 Massachusetts Medical Society.



**Figure 1.** Mean Blood Pressure According to Age and Race or Ethnic Group in U.S. Adults.

Data are from Burt et al.<sup>3</sup>

arterial stiffening and impair endothelium-dependent vasodilatation.<sup>11,12</sup>

Despite the well-recognized benefits of blood-pressure reduction, in the most recent U.S. National Health Survey (2003–2004), only 37% of patients being treated for hypertension had blood-pressure levels below 140/90 mm Hg.<sup>2</sup> The low control rate is largely attributable to inadequate management of systolic hypertension.<sup>1,3</sup>

## STRATEGIES AND EVIDENCE

### EVALUATION

The initial evaluation of the patient with systolic hypertension should include an assessment for the presence of other cardiovascular risk factors, end-organ damage, concomitant diseases affecting prognosis and treatment, identifiable causes of hypertension (e.g., hyperthyroidism), and potentially contributing lifestyle factors (diet and exercise).<sup>1</sup> Physical examination should include assessment of optic fundi, thyroid, heart, lungs, kidneys, peripheral pulses, and the neurologic system, with attention to signs of aortic insufficiency, hyperthyroidism, or Paget's disease of bone. In rare cases, peripheral arteries may become so rigid that measuring blood pressure with the standard arm cuff may lead to an overestimate of arterial pressure because of incomplete compression of the brachial artery.<sup>13</sup> Such pseudohyper-

tension should be considered particularly in those patients whose hypertension does not respond to therapy as expected or who have postural symptoms with treatment.

Routine laboratory and electrocardiographic studies should be performed to evaluate cardiovascular risk. Laboratory tests should include urinalysis, measures of blood glucose and hematocrit, serum potassium level, estimated glomerular filtration rate,<sup>14</sup> and lipoprotein profile.

### EVIDENCE SUPPORTING TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION

Several clinical trials have shown the cardiovascular benefits of reducing systolic pressure in patients with isolated systolic hypertension. In the Systolic Hypertension in the Elderly Program (SHEP), treatment with the diuretic agent chlorthalidone for an average of 4.5 years in patients with systolic blood pressure of 160 mm Hg or greater and diastolic pressure below 90 mm Hg resulted in impressive reductions in the incidence of stroke (–36%), coronary heart disease (–27%), and congestive heart failure (–55%), as compared with placebo.<sup>15</sup> Two large clinical trials using the calcium-channel blocker nitrendipine in patients with isolated systolic hypertension showed benefits broadly similar to those seen in the SHEP trial. In the European Trial in Systolic Hypertension and in the Systolic Hypertension in China

Trial, treatment was associated with decreases in the incidence of stroke (−42 and −38%, respectively), coronary heart disease (−30 and −6%), and congestive heart failure (−29 and −58%).<sup>16,17</sup> A meta-analysis of eight trials involving several drug regimens in patients 60 years of age or older with systolic pressure of 160 mm Hg or greater and diastolic pressure below 95 mm Hg showed that antihypertensive therapy administered for an average of 3.8 years reduced total mortality by 13% and mortality due to cardiovascular disease by 18%. In addition, all complications of cardiovascular disease were reduced by 26%, stroke by 30%, and coronary heart disease events by 23%.<sup>18</sup>

## MANAGEMENT

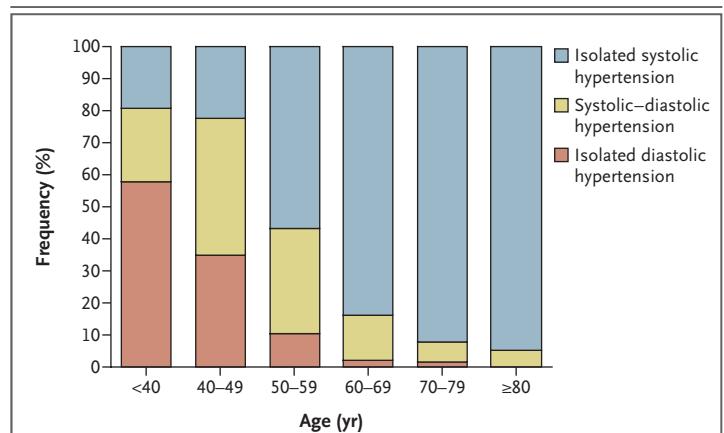
The therapeutic approach and goals for isolated systolic hypertension are similar to those recommended for most other types of hypertension (Fig. 3).<sup>1,9</sup> The recommended target level of blood pressure is below 140/90 mm Hg, except in patients with diabetes or chronic renal disease, for whom a lower goal (130/80 mm Hg or lower) is advised.

### LIFESTYLE CHANGES

The lifestyle modifications recommended for patients with isolated systolic hypertension are the same as those for patients with other forms of hypertension,<sup>1,19</sup> including weight reduction, restriction of dietary sodium, adoption of the Dietary Approaches to Stop Hypertension (known as DASH) eating plan (a diet rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat), increased physical activity, and moderation of alcohol intake (no more than the equivalent of two drinks per day for men and one for women). These interventions not only reduce blood pressure but also favorably affect other risk factors for cardiovascular disease, such as the dyslipidemia, abdominal obesity, and diabetes that characterize the metabolic syndrome.<sup>20</sup>

### DRUG TREATMENT

Five major classes of antihypertensive drugs are most useful: diuretics,  $\beta$ -adrenergic blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers, and calcium-channel blockers. Each has been shown in clinical trials to reduce cardiovascular events.<sup>15-17,21-24</sup> When used in recommended dosages, their mean effects on blood pressure are similar,<sup>25</sup> although indi-

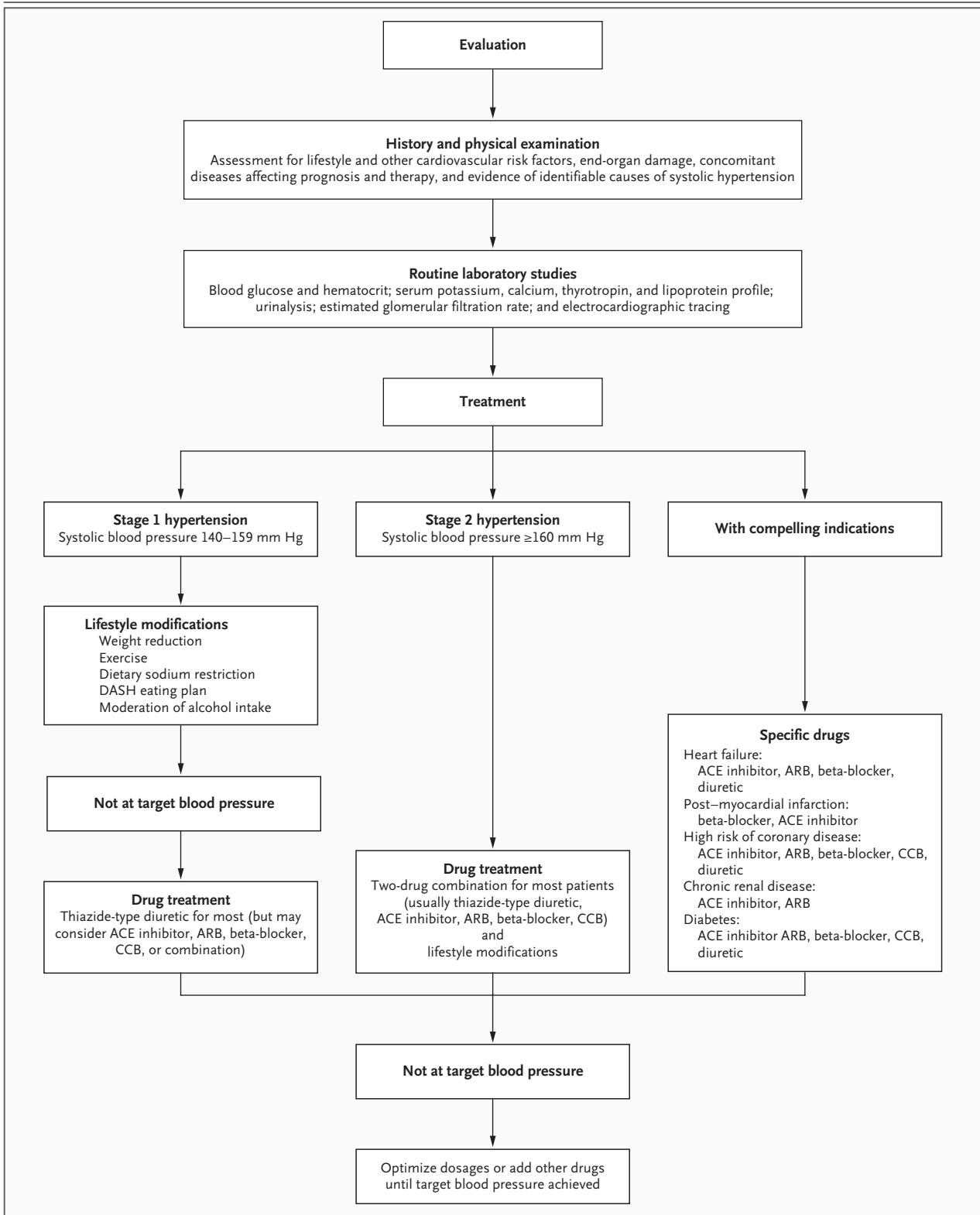


**Figure 2.** Frequency of Untreated Hypertension According to Subtype and Age. Data are from Franklin et al.<sup>5</sup>

vidual patients may have different responses to each drug. In approximately two thirds of patients with hypertension, two or more drugs will be required to achieve target blood-pressure levels.

The current Joint National Committee guidelines<sup>1</sup> recommend thiazide diuretics as initial drug therapy for most patients with hypertension, on the basis of their proven efficacy in reducing blood pressure and cardiovascular complications in clinical trials and their low cost. Other antihypertensive medications are preferred initially when there are certain coexisting conditions. For example, in patients with hypertension and chronic kidney disease, compelling evidence from clinical trials supports the use of either an ACE inhibitor or an angiotensin-receptor blocker,<sup>26-28</sup> and for patients who have had myocardial infarction or heart failure, a beta-blocker and an ACE inhibitor are preferred.<sup>29,30</sup> Elderly men with both hypertension and benign prostatic hypertrophy are often treated for urinary symptoms with an  $\alpha$ -1-receptor antagonist, which can help control the hypertension but may increase the risk of orthostatic hypotension. Nevertheless, despite some important differences between antihypertensive medications, the major benefits of therapy are related to the reduction of blood pressure rather than to other specific drug actions.

Thiazide-type diuretics can induce carbohydrate intolerance and diabetes,<sup>31</sup> effects that are greater in patients in whom hypokalemia develops.<sup>32</sup> However, the clinical importance of such adverse effects is uncertain, given clinical trial data showing that thiazides are at least as effec-



**Figure 3. Management of Isolated Systolic Hypertension.**

DASH denotes Dietary Approaches to Stop Hypertension, ACE angiotensin-converting-enzyme, ARB angiotensin-receptor blocker, and CCB calcium-channel blocker. Adapted from Chobanian et al.<sup>1</sup>

tive as other drug classes in reducing the risk of complications from cardiovascular disease.<sup>22,33</sup> The current debate over initial drug use notwithstanding, most patients with hypertension should end up receiving a diuretic as part of their regimen, since more than one drug is usually required to achieve blood-pressure control and since diuretics complement the action of the other drugs so well.

The use of beta-blockers as first-line therapy for elderly patients with hypertension has been questioned recently. A meta-analysis of intervention trials for hypertension showed a 16% higher incidence of stroke among patients treated with traditional beta-blockers (primarily atenolol) than among those treated with other antihypertensive medications.<sup>34</sup> The lesser benefit from beta-blockers could be related to a smaller reduction in blood pressure. In a recent study of patients treated with atenolol, blood pressure measured by standard cuff techniques overestimated the pressure reduction by 4.5 mm Hg as compared with aortic pressure calculated from applanation tonometry and radial-artery waveforms<sup>35</sup>; in contrast, with a calcium-channel blocker, ACE inhibitor, or diuretic agent, the effects on central aortic- and brachial-artery pressures were similar.<sup>36</sup>

Initial therapy with beta-blockers in elderly patients should probably be limited to those with compelling indications, such as coronary heart disease, myocardial infarction, congestive failure, or certain arrhythmias. No data are available yet on whether such restrictions should apply to the newer beta-blockers with peripheral vasodilator properties.

#### STRATEGIES FOR IMPROVING BLOOD-PRESSURE CONTROL

Inertia on the part of physicians and a reluctance to treat systolic hypertension are important factors limiting optimal control of blood pressure.<sup>37</sup> Many physicians do not give adequate doses of antihypertensive medications or do not use a combination of drugs to achieve the target pressure. Factors that adversely affect adherence to treatment include inadequate patient education, physician empathy, and social support; the presence of coexisting diseases; complex dose regimens; problems with transportation of the patient; and the cost of medications.<sup>9</sup> Participation by ancillary staff, including nurse clinicians, physicians' assistants, and pharmacists, has been shown to be effective in improving blood-pressure control.<sup>38</sup>

Most elderly patients tolerate antihypertensive medications well, although a low starting dose and a gradual rate of increase in the dose (e.g., every 2 to 4 weeks) is prudent, particularly in frail and relatively immobile patients and in patients with diabetes, since both groups are at increased risk for orthostatic hypotension and associated falls.<sup>39,40</sup>

---

#### GUIDELINES

---

The Joint National Committee guidelines, which have been endorsed by several professional organizations, including the American Medical Association, the American Heart Association, and the American Society of Hypertension, recommend thiazide-type diuretics as initial drug therapy for most patients with isolated systolic hypertension unless there are specific contraindications for their use.<sup>1</sup> Compelling indications discussed above warrant initiation of therapy with an ACE inhibitor, angiotensin-receptor blocker, calcium-channel blocker, or beta-blocker. The addition of a drug from another class is required if the target blood pressure is not achieved (Fig. 3).

The joint guidelines of the European Society for Hypertension and the European Society of Cardiology do not give preference to diuretics and recommend any of the five major classes of antihypertensive drugs for first-line therapy.<sup>41</sup> Recent guidelines from Great Britain argue against the use of both diuretics and beta-blockers for initial therapy and favor ACE inhibitors, angiotensin-receptor blockers, or calcium-channel blockers.<sup>42</sup> Despite some differences in recommendations, all of these guidelines emphasize that the major benefits of therapy are related to lowering blood pressure and controlling hypertension.

---

#### AREAS OF UNCERTAINTY

---

Whether lowering diastolic blood pressure is harmful to some patients with isolated systolic hypertension is uncertain. Myocardial perfusion occurs during diastole, and excessive reduction of diastolic pressure could be detrimental in those with coronary artery disease. Several studies have suggested that a diastolic pressure below 60 mm Hg, particularly in patients with documented coronary disease, may be associated with an increased risk of myocardial infarction and death (the so-called J-curve phenomenon).<sup>43-46</sup> However, a meta-analysis of clinical trials indicated that the in-

creased risk of coronary events at low diastolic pressure was not related to the treatment or the pressure levels and was probably explained by serious illnesses that were causing the low blood pressure.<sup>47</sup> Although reducing diastolic pressure to very low levels might be harmful in some cases, the overall benefits of antihypertensive therapy in patients with isolated systolic hypertension, including the reduction in coronary heart disease, are well documented.

The effects of treating hypertension in patients older than 80 years of age are unclear because few intervention studies have been performed in hypertensive patients in this age group. In a prospective observational study of 85-year-old patients followed for approximately 4 years, those with the lowest blood pressures had the highest mortality,<sup>48</sup> but this result might reflect confounding by poor health status. In the pilot phase of the Hypertension in the Very Elderly Trial, whose subjects had an average age of 84 years at enrollment, the incidence of stroke after 13 months was 53% lower among subjects receiving a thiazide diuretic or lisinopril than among those receiving placebo; however, total mortality was 23% higher with treatment (not a significant difference).<sup>49</sup> The full study is in progress. A similar trend toward increased mortality with antihypertensive therapy has been apparent in other small trials involving the very old.<sup>50</sup> In a study of ambulatory patients 80 years of age or older whose blood pressure was controlled to levels below 140/90 mm Hg, patients with lower blood-pressure levels had lower 5-year survival rates than did those with higher blood pressures.<sup>51</sup>

The effect of antihypertensive therapy on the incidence of dementia is also uncertain. In the Systolic Hypertension in Europe trial, the incidence of dementia was approximately 50% lower among drug-treated patients than among controls.<sup>52</sup> The favorable effect of treatment appeared to be related in part to the reduction in the incidence of stroke. No significant effect of therapy on cognition was evident in the SHEP trial.<sup>53</sup> However, observational data from the Honolulu-Asia Aging Study of Japanese-American men suggested that the risks of dementia and Alzheimer's disease were lower among the men who were treated for hypertension than among those with untreated hypertension, and the differences increased with an increased duration of therapy.<sup>54</sup> It is reassuring that no deterioration of mental function was noted in these trials.

No intervention studies have been conducted to assess the benefits of treatment in patients with systolic blood pressure between 140 and 159 mm Hg. The treatment recommendations for this group are based primarily on epidemiologic data demonstrating a substantial increase in the risk of cardiovascular disease.

In untreated elderly patients with hypertension, pulse pressure (the difference between systolic and diastolic pressure) has been reported to be a better indicator of the risk of cardiovascular disease than systolic blood pressure.<sup>55</sup> However, its added usefulness in predicting risk appears to be minimal, and no clinical trial data are available on the benefits of reducing pulse pressure.

---

#### CONCLUSIONS AND RECOMMENDATIONS

---

Isolated systolic hypertension is a major risk factor for cardiovascular disease and renal disease, and abundant data are available to justify intensive efforts to manage systolic pressure. In most older patients, elevation of systolic blood pressure occurs because of reduced elasticity of conduit arteries. Initial evaluation can generally be limited to assessment of lifestyle and identification, by means of the history, physical examination, and routine laboratory tests, of concomitant disorders that influence prognosis and therapy. The patient described in the case vignette has stage 2 hypertension (systolic blood pressure  $\geq 160$  mm Hg), and prompt initiation of drug treatment is appropriate. Nonpharmacologic interventions should also be recommended and can reduce the number and dosage of blood-pressure medications required. I would treat his hypertension initially with a thiazide-type diuretic, unless the workup reveals a compelling indication for use of another antihypertensive drug. Initial follow-up can be carried out at approximately monthly intervals until the target blood pressure of less than 140/90 mm Hg is achieved. If a second or third drug is required, an ACE inhibitor, angiotensin-receptor blocker, calcium-channel blocker, or beta-blocker can be added; the choice will depend on the patient's clinical status and the clinician's experience. A tablet combining the selected drugs is often desirable.

Once the target blood pressure is achieved, follow-up can occur every 3 to 6 months, unless coexisting conditions require more frequent assessment. Serum potassium, creatinine, and blood

glucose levels should be measured at least annually. Low serum potassium levels should be managed with potassium supplementation, use of a potassium-sparing diuretic, or both. Other risk factors for cardiovascular disease should be treated to achieve target levels, and smokers should

be urged to participate in a smoking-cessation program.

Dr. Chobanian reports receiving a lecture fee from Shionogi. He reports serving as chair for the Seventh Report of the Joint National Committee, which developed guidelines for the management of hypertension. No other potential conflict of interest relevant to this article was reported.

## REFERENCES

- Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003;289:2560-72. [Erratum, *JAMA* 2003;290:197.]
- Ong KL, Cheung BMY, Man YB, Lau CP, Lam KSL. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007;49:69-75.
- Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25:305-13.
- Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291-7.
- Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* 1997;96:308-15.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13. [Erratum, *Lancet* 2003;361:1060.]
- Kannel WB, D'Agostino RB, Sullivan L, Wilson PWF. Concept and usefulness of cardiovascular risk profiles. *Am Heart J* 2004;148:16-26.
- Izzo JL, Levy D, Black HR. Importance of systolic blood pressure in older Americans. *Hypertension* 2000;35:1021-4.
- Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.
- Yambe M, Tomiyama H, Yamada J, et al. Arterial stiffness and progression to hypertension in Japanese male subjects with high normal blood pressure. *J Hypertens* 2007;25:87-93.
- Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:932-43.
- Lind L. Systolic and diastolic hypertension impair endothelial vasodilatory function in different types of vessels in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *J Hypertens* 2006;24:1319-27.
- Spence JD, Sibbald WJ, Cape RD. Pseudohypertension in the elderly. *Clin Sci Mol Med Suppl* 1978;55:399s-402s.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-64.
- Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64.
- Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older patients with isolated systolic hypertension. *J Hypertens* 1998;16:1823-9.
- Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865-72. [Erratum, *Lancet* 2001;357:724.]
- Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effect of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med* 2001;161:685-93.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. *Circulation* 2002;106:3143-421.
- Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281-5.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97. [Errata, *JAMA* 2003;289:178, 2004;291:2196.]
- Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002;359:995-1003.
- Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348:583-92.
- Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003;326:1427-31.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62. [Erratum, *N Engl J Med* 1993;330:152.]
- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina — summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159-68.
- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary — a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure: developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure

- Society of America). *Circulation* 2001;104:2996-3007.
31. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007;369:201-7. [Erratum, *Lancet* 2007;369:1518.]
32. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006;48:219-24.
33. Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity: the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6.
34. Lindholm LH, Carlberg B, Samuelsson O. Should  $\beta$  blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;366:1545-53.
35. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113:1213-25.
36. Dart AM, Cameron JD, Gatzka CD, et al. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. *Hypertension* 2007;49:1242-7.
37. Hyman DJ, Pavlik VN, Vallbona C. Physician role in lack of awareness and control of hypertension. *J Clin Hypertens* 2000;2:324-30.
38. Hill MN, Miller NH. Compliance enhancement: a call for multidisciplinary approaches. *Circulation* 1996;93:4-6.
39. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. *Am J Med* 2000;108:106-11.
40. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998;98:2290-5.
41. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53. [Errata, *J Hypertens* 2003;21:2203-4; 2004;22:435.]
42. Hypertension: management of hypertension in adults in primary care; partial update of NICE Clinical Guideline 18. London: National Institute for Health and Clinical Excellence, 2006.
43. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987;1:581-4.
44. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med* 1999;159:2004-9.
45. Zanchetti A, Hansson L, Clement D, et al. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? *J Hypertens* 2003;21:797-804.
46. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884-93.
47. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002;136:438-48.
48. van Bommel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006;24:287-92.
49. Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. *J Hypertens* 2003;21:2409-17.
50. Gueyffier F, Bulpitt C, Boissel J-P, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomized controlled trials. *Lancet* 1999;353:793-6.
51. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood pressure and survival in the oldest old. *J Am Geriatr Soc* 2007;55:383-8.
52. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347-51.
53. Di Bari M, Pahor M, Franse LV, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the Systolic Hypertension in the Elderly Program (SHEP) trial. *Am J Epidemiol* 2001;153:72-8.
54. Peila R, White LR, Masaki K, Petrovich H, Launer LJ. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke* 2006;37:1165-70.
55. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 1999;100:354-60.

Copyright © 2007 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The Journal's Web site ([www.nejm.org](http://www.nejm.org)) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronological order, with the most recent first.