CLINICAL PRACTICE

Resistant or Difficult-to-Control 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 authors' clinical recommendations.*

A 70-year-old woman with a long-standing history of hypertension comes for follow-up. Her medications include atenolol (100 mg daily), hydrochlorothiazide (12.5 mg daily), lisinopril (40 mg daily), and ibuprofen (400 mg twice daily for osteoarthritis). She does not smoke or drink alcohol. Her body-mass index (the weight in kilograms divided by the square of the height in meters) is 32. Her systolic and diastolic blood pressures (measured three times while she was seated) range from 164 to 170 mm Hg and 92 to 96 mm Hg, respectively, and the pulse rate is 72 per minute. Examination of her ocular fundi reveals arteriolar narrowing. The results of cardiovascular examination are normal. There are no abdominal bruits. The serum potassium level is 3.8 meq per liter, and the serum creatinine level is 1.2 mg per deciliter (106 μmol per liter); there is no microalbuminuria. How should this patient be further evaluated and treated?

THE CLINICAL PROBLEM

Resistant, or refractory, hypertension is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes or renal disease (i.e., with a creatinine level of more than 1.5 mg per deciliter [133 μmol per liter] or urinary protein excretion of more than 300 mg over a 24-hour period), despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic.[1] Patients who have recently received a diagnosis of hypertension or who have not yet received treatment should not be considered to have resistant hypertension, regardless of their blood-pressure level.

Data on the prevalence of resistant hypertension are scant. In large clinical trials of hypertension[2,3] in which protocols required drug titration until the blood pressure was below a predefined target, the diastolic blood pressure was below 90 mm Hg in approximately 90 percent of patients, but the systolic blood pressure was below 140 mm Hg in only 60 percent of patients. However, patients who had no predefined response to treatment did not meet all of the criteria for resistant hypertension as cited above. In one specialty hypertension clinic, only 59 percent of patients whose hypertension was considered to be resistant had blood pressures below 140/90 mm Hg despite careful drug titration.[4] These observations suggest that blood-pressure goals may be difficult to achieve in as many as 40 percent of patients. Resistant or difficult-to-control systolic hypertension is more common in patients over the age of 60 years than in younger patients.[5]

Patients whose hypertension is uncontrolled are more likely to have target-organ damage and a higher long-term cardiovascular risk than are patients whose blood pressure is controlled.[6] Heart failure, stroke, myocardial infarction, and renal failure are related to the degree of the elevation in blood pressure. Other risk factors,

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such as diabetes and dyslipidemia, further increase the cardiovascular risk in these patients.

This article focuses on the evaluation and management of resistant hypertension as well as difficult-to-control hypertension, which is defined here as persistently elevated blood pressure despite treatment with two or three drugs but not meeting the above-mentioned strict criteria for resistant hypertension. Difficult-to-control hypertension is far more common than resistant hypertension.[5]

STRATEGIES AND EVIDENCE

Formal studies of the management of resistant or difficult-to-control hypertension are few, and strategies are based largely on observational data from specialty clinics.[7,8] These series and clinical experiences suggest that a careful evaluation of a patient's adherence to and adequacy of therapy and lifestyle factors often reveals modifiable contributors to refractory blood pressure; secondary causes (including exogenous substances) must also be considered. A suboptimal medical regimen has been shown to be the primary cause of resistant hypertension in a majority of patients in these studies. Figure 1 outlines a suggested approach to evaluation.

DIAGNOSIS

Blood pressure should be measured after a patient has been seated quietly for five minutes, with his or her arm supported at heart level and with the use of a properly calibrated and sized cuff. If the cuff is too narrow or too short, readings may be erroneously high (typically by 5 to 15 mm Hg in the case of systolic pressure). The patient should be asked whether he or she has smoked a cigarette within the previous 15 to 30 minutes, since smoking can cause an elevation in systolic blood pressure of 5 to 20 mm Hg. Avoidance of coffee is also recommended, although the increase in systolic blood pressure after one cup of caffeinated coffee is usually only 1 to 2 mm Hg. Long-term smoking or coffee drinking does not cause persistently elevated blood pressure.[9,10]

The diagnosis is based on the findings of at least two or three elevated blood-pressure measurements (in the physician's office or at home), despite adherence to regimens containing three medications. However, if the blood pressure is above 160/100 mm Hg, additional readings are not necessary for diagnosis.[1] Evaluation (including physical examination and laboratory testing) is routinely warranted to look for evidence of end-organ damage related to hypertension (Table 1) and for other cardiovascular risk factors.[1] Volume overload and elevated sympathetic tone, which are common in patients with uncontrolled blood pressure, may occasionally be suggested by the presence of a rapid pulse rate.[12] Renin levels have not been found to be useful in the prediction of excess volume, though they may be useful in the evaluation of possible secondary causes of hypertension.

Some patients who have what appears to be resistant hypertension have a normal blood pressure at home. This phenomenon has been attributed to transitory, or "white-coat," resistant hypertension in the physician's office. Repeated home measurements or 24-hour ambulatory monitoring may differentiate this type of hypertension from truly resistant hypertension.[13] Such measures are warranted in patients undergoing treatment who have consistently high blood-pressure levels in the physician's office yet have no evidence of target-organ damage. In one study, as many as a third of patients with apparently resistant hypertension had average blood-pressure levels of less than 130/85 mm Hg on 24-hour or home measurement.[14] Some data suggest that blood-pressure values obtained at home or during 24-hour ambulatory procedures correlate better with target-organ involvement, especially left ventricular hypertrophy, than do values obtained in the physician's office.[15] However, office, or white-coat, hypertension is not benign and should not be ignored.

Rarely, in older patients, what appears to be refractory hypertension may represent inaccurate measurement owing to severely sclerotic arteries (i.e., pseudohypertension). The condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (the Osler maneuver),[16] although this sign is not specific. The presence of this condition can be confirmed by intra-arterial blood-pressure measurement.

Adherence to Treatment

Because a diagnosis of resistant hypertension requires a finding of elevated blood pressure despite the use of adequate doses of at least three medications, the patient's adherence to therapy and

the adequacy of the dose should be evaluated routinely. Studies have reported that medication was not increased in more than 50 percent of patients with poorly controlled hypertension despite repeated office visits.[17] Some patients take less than the prescribed dose of medication for economic or other reasons. However, side effects have not been found to be an important reason for a lack of adherence to therapy but may contribute to nonadherence. Signs suggesting nonadherence include missed office visits and a lack of physiological evidence of therapy (e.g., rapid heart rate despite the prescription of beta-blockers or verapamil), but nonadherence is often difficult to recognize or exclude objectively.[13]

Interfering or Exogenous Substances

Patients should be asked routinely about the use of medications or other substances that can elevate blood pressure or antagonize the effects of antihypertensive drugs. These substances include sympathomimetic drugs (e.g., ephedra, phenylephrine, cocaine, and amphetamines), herbal supplements (e.g., ginseng and yohimbine), anabolic steroids, appetite suppressants, and erythropoietin, although all these drugs probably account for less than 2 percent of cases of resistant hypertension.[18] Nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors may raise both systolic and diastolic blood pressure by several mm Hg.[19] These agents impair the excretion of sodium, which causes volume retention; they also inhibit the production of local renal vasodilative prostaglandins; the therapeutic action of angiotensin-converting–enzyme (ACE) inhibitors and loop diuretics (but not calcium-channel blockers) depends on the availability of these prostaglandins.[19,20] Efforts should be made to discontinue such agents, although if they are needed for another condition, antihypertensive therapy may need to be modified.

An assessment of dietary and lifestyle factors is also important. Excessive alcohol use (more than three or four drinks per day)[21] and a high sodium intake (typically defined by a urinary sodium excretion of more than 150 mmol per day) may contribute to resistant hypertension; the frequency of salt sensitivity is increased among patients who are at least 60 years of age, patients who are black or obese, and patients with renal impairment.[22] Studies indicate that more than 40 percent of patients with resistant hypertension are obese,[23,24] and obese patients may require higher doses of antihypertensive medications than do nonobese patients.

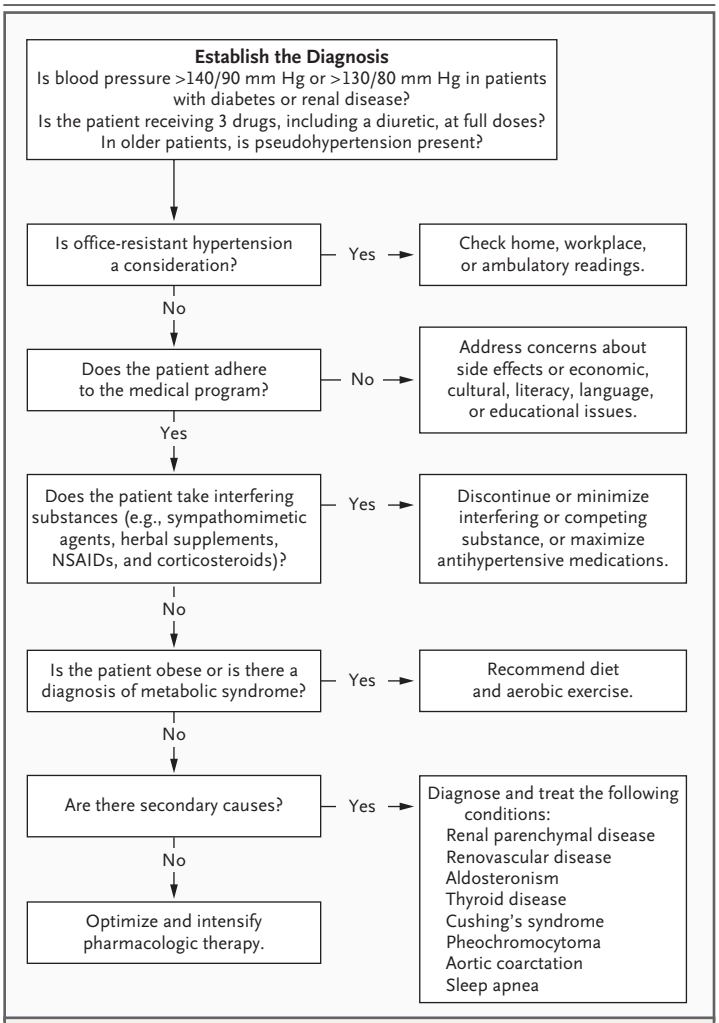

Figure 1. Treatment of Resistant Hypertension.

NSAIDs denotes nonsteroidal antiinflammatory drugs.

Evaluation of Secondary Hypertension

The possibility that an underlying condition is causing hypertension must also be considered; secondary hypertension is often unmanageable until the underlying cause is treated.[11] Among 4000 patients with resistant hypertension who were evaluated during an 18-year period at one tertiary center, secondary causes were found in 10 percent of patients overall and in 17 percent of patients over the age of 60 years.[25]

Chronic renal parenchymal disease, usually resulting from diabetic nephropathy or hyperten-

Table 1. Recommended Evaluation of Patients with Hypertension.*

Basic studies
History taking and physical examination (with a particular focus on the identification of cardiac enlargement, abdominal bruits, peripheral pulses, and funduscopic changes)
Urinalysis (for evidence of microalbuminuria)
Blood chemical analysis, including creatinine, blood glucose, potassium, uric acid, and lipids
Electrocardiography
Additional studies in patients with resistant or difficult-to-treat hypertension
Repeated measurement of home or ambulatory blood pressures
Echocardiography
Consideration of tests for causes of secondary hypertension

* Data are adapted from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[1] and Wofford et al.[11]

sive nephrosclerosis, may be the most common cause of secondary hypertension. Atherosclerotic renovascular disease, which is particularly prevalent among elderly smokers, is another possible cause. The presence of an abdominal bruit or hypokalemia or a recent increase in the severity of hypertension may suggest the diagnosis of atherosclerotic renovascular disease. Screening for renovascular disease may be warranted if other causes of resistant hypertension are not identified, since angioplasty and stenting may improve blood pressure. However, in cases of renovascular hypertension caused by atherosclerotic disease, blood pressure often remains high even after intervention, in contrast to hypertension caused by the much less common fibromuscular dysplasia.[26]

Table 2 summarizes features of and screening tests for these and other causes of secondary hypertension, such as primary aldosteronism (considered to be more common than previously recognized), pheochromocytoma, and sleep apnea (recently recognized to be associated with refractory hypertension).[27,28] Generally, the decision to screen a patient for such disorders should depend on suggestive findings on history taking, physical examination, or basic laboratory testing. Interventions that are directed at these disorders (e.g., surgery or aldosterone-antagonist therapy for hyperaldosteronism, surgery for pheochromocytoma, and continuous positive airway pressure for sleep apnea[29]) may substantially decrease, although not always normalize, blood pressure. A detailed discussion of all the causes of secondary hypertension is beyond the scope of this article but is available elsewhere.[30]

TREATMENT

Patients should routinely be encouraged to reduce their intake of sodium, lose weight (if appropriate), engage in moderate exercise, and reduce their intake of alcohol (to no more than two to three drinks per day). The degree of blood-pressure lowering expected with each of these approaches is often modest but clinically important — for example, 2 to 8 mm Hg with dietary sodium restriction (with a goal of urinary sodium excretion of less than 100 mmol per day), 2 to 4 mm Hg with reduced alcohol consumption, and 4 to 9 mm Hg with regular physical activity (such as walking briskly for 30 to 45 minutes daily).

Adherence to therapy may be increased by the initiation of a system of follow-up reminders or telephone contacts. The involvement of nurses or nurse practitioners, who may have more time than a physician to discuss potential side effects of medications, has been shown to improve patients' control of their blood pressure.[31] The use of combination therapy (two medications in one pill) may also improve adherence and, in some cases, may reduce the cost of care.[32]

Few data from randomized trials are available to guide the choice of regimen for patients whose blood pressure remains high even though they take several medications; recommendations are based largely on physiological principles and clinical experience. Because volume overload is common among such patients, the most important therapeutic maneuver is generally to add or increase diuretic therapy; more than 60 percent of patients with resistant hypertension may have a response to this approach.[8,12,18,33] Thiazide di-

Table 2. Secondary Causes of Resistant Hypertension.*

Secondary Cause	Symptoms and Signs	Estimated Prevalence	Screening Tests or Findings	Treatment
		%		
Renal parenchymal disease	Nocturia, edema	1.0–8.0 (depending on the creatinine level)	Proteinuria, cells, and casts; elevated levels of serum creatinine	ACE inhibitor or ARB plus loop diuretic; beta-blocker; calcium-channel blocker
Renal artery disease	Recent onset of elevated blood pressure in older patients or hypertension in patients under 5 yr; loss of previously good blood-pressure control; use of tobacco; widespread vascular disease; multidrug-resistant hypertension; severe hypertension in young patients; epigastric or abdominal bruit	3.0–4.0	Increased serum creatinine level during treatment with an ACE inhibitor or ARB; MRA; Doppler; ACE-inhibitor renography; disparity in kidney size	Angioplasty with stenting in patients with unilateral disease and in selected patients with bilateral disease; balloon angioplasty for fibromuscular dysplasia; ACE inhibitor or ARB with diuretic
Aldosteronism	Fatigue; hypokalemia (not always present); lack of response to potassium supplementation	1.5–15.0 (higher in recent series)	Abnormal ratio of aldosterone to renin (>25:1); abnormal response to sodium loading; imaging studies (CT or MRI)	Aldosterone antagonists; ACE inhibitor or ARB with hyperplasia; surgery for adenoma
Pheochromocytoma	Palpitations; headache; diaphoresis; paroxysms of hypertension	<0.5	Abnormal urinary catecholamine excretion (including norepinephrine, >80 μg/24 hr, and VMA, >5 mg/24 hr); plasma metanephrines; imaging studies (CT or MRI)	Alpha-adrenergic inhibitor; beta-blocker; surgical removal
Cushing's syndrome	Obesity; striae; muscle weakness; increased serum glucose level; fluid retention	<0.5	Increased levels of urinary cortisol (>55 μg/24 hr); positive results on a dexamethasone suppression test; imaging studies (CT or MRI)†	Surgical intervention
Hyperthyroidism or hypothyroidism	Tachycardia; weight loss; anxiety (in hyperthyroidism); weight gain; fatigue (in hypothyroidism)	1.0–3.0	Increased systolic blood pressure (hyperthyroidism); increased diastolic blood pressure (hypothyroidism)	Treatment of underlying disorders
Sleep apnea	Interrupted sleep; snoring; daytime somnolence; obesity	NA	Sleep studies	Weight loss; continuous positive airway pressure; possibly, aldosterone antagonists
Coarctation of the aorta	Brachial or femoral pulse differential; systolic bruits (back and chest)	<1.0	Echocardiography; imaging studies (CT or MRI)	Surgery; balloon angioplasty

* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA magnetic resonance angiography, VMA vanillylmandelic acid, CT computed tomography, MRI magnetic resonance imaging, and NA not available.

† Positive results on a dexamethasone suppression test denote an absence of the lowering of plasma cortisol levels below 3 μg per deciliter after the administration of 1 mg of dexamethasone.

uretics are effective in doses of 12.5 to 25.0 mg daily if renal function is normal. Experience suggests that a daily dose of 25 to 50 mg will result in a further decrease in blood pressure. If the glomerular filtration rate is below 30 to 50 ml per minute (or the serum creatinine level is more than 1.5 mg per deciliter), loop diuretics should be used. Short-acting loop diuretics, such as furosemide (at a dose of 20 to 80 mg daily) or bumetanide (at a dose of 0.5 to 2.0 mg daily), must be given two or three times per day.[34] Intermittent natriuresis with once-daily drug administration may lead to reactive sodium retention mediated by the renin–angiotensin system, with consequent inadequate blood-pressure control. Longer-acting diuretics such as torsemide (at 2.5 to 5.0 mg) may be given once a day but are more expensive.

A generally useful strategy is to combine agents from various classes, each of which has one or more of the following effects: a reduction in volume overload (diuretics and aldosterone antagonists), a reduction in sympathetic overactivity (beta-blockers), a decrease in vascular resistance (through the inhibition of the renin–angiotensin system with the use of ACE inhibitors or angiotensin-receptor blockers), the promotion of smooth-muscle relaxation (dihydropyridine calcium-channel blockers and alpha-blockers), and direct vasodilation (hydralazine and minoxidil), although the latter are less well tolerated. An additional medication with a different mechanism of action from others the patient is receiving may further lower the blood pressure or overcome compensatory changes in blood-pressure elevation caused by the first medication without increasing adverse effects. For example, adding a beta-blocker or ACE inhibitor may counteract the stimulation of the renin–angiotensin system by diuretics.[34]

Some logical combinations include a diuretic with an ACE inhibitor, a beta-blocker, or an angiotensin-receptor blocker or an ACE inhibitor with a calcium-channel blocker. Most patients with resistant hypertension are already receiving combinations of these agents. In these instances, it may be necessary to increase the dose or the frequency of administration from once to twice daily or to include an additional drug, such as an aldosterone antagonist if a patient is already receiving a diuretic, an ACE inhibitor, and a calcium-channel blocker. Certain medications may be preferred if the patient has coexisting illnesses (Table 1 of the Supplementary Appendix, which is available with the full text of this article at www.nejm.org). For example, the addition of an angiotensin-receptor blocker, a beta-blocker, or an aldosterone antagonist would be reasonable if the drug is not already being used in a patient with heart failure.

Figure 2 summarizes one approach to the optimization of drug therapy in patients with resistant hypertension. There are limited data to guide whether some agents should be stopped before others are added if multiple drugs are inadequate.

Combined alpha- and beta-blockers (labetalol and carvedilol) may improve blood-pressure control. Centrally acting agents — for example, clonidine, α_2-adrenergic blockers, reserpine (in low doses), and direct vasodilators (hydralazine or, in rare cases, minoxidil) — may be necessary in some cases, as tolerated. With direct vasodilators, concomitant high-dose beta-blockers (metoprolol or atenolol) and loop diuretics (furosemide) will be needed to counteract reflex tachycardia and edema. Aside from the aldosterone antagonist spironolactone and alpha-blockers, which have been shown to reduce blood pressure in patients with resistant hypertension, data are lacking to predict the magnitude of further blood-pressure reduction associated with the addition of one of these other medications; clinical experience suggests a decrease in systolic pressure of about 5 to 10 mm Hg.

Referral to a hypertension specialist should be considered in patients whose hypertension is difficult to control despite an assessment of adherence, dose, and other factors that may exacerbate the condition — particularly if the use of the above-mentioned combinations is not helpful. In truly refractory cases, other combinations of medications may be considered. Combinations that have been studied include dual diuretic therapy (spironolactone at a dose of 25 to 50 mg daily plus a thiazide at a dose of 12.5 to 50 mg daily or a loop diuretic), which has been associated with a reduction in systolic blood pressure of 20 to 25 mm Hg and in diastolic pressure of 10 to 12 mm Hg (larger decreases than those obtained with the use of a single diuretic)[27]; dual calcium-channel blockers (a dihydropyridine, such as amlodipine, plus a nondihydropyridine), which has been associated with a reduction in systolic blood pressure of 6 mm Hg and a reduction in diastolic pressure of 8 mm Hg, as compared with

nifedipine alone[35]; and a combination of an ACE inhibitor and an angiotensin-receptor blocker, which has been associated with a reduction in systolic blood pressure of 5 to 6 mm Hg, as compared with either agent alone.[36] However, the risks of such regimens must be considered (e.g., hyperkalemia with the ACE inhibitor plus an angiotensin-receptor blocker).

GUIDELINES

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the need to consider secondary causes, improper blood-pressure measurement, volume overload, competing substances, obesity, nonadherence to treatment, inadequate doses or inappropriate combinations of medications, and alcohol consumption as factors in resistant hypertension.[1] These guidelines do not include specific recommendations regarding when or how to evaluate patients for specific secondary causes of resistant hypertension or for the management of truly resistant cases.

AREAS OF UNCERTAINTY

Several questions require further investigation.[37] The true prevalence of resistant hypertension remains uncertain. More information is needed to determine the optimal evaluation of patients for secondary hypertension, including indications for screening for hyperaldosteronism, which appears to be underdiagnosed. Data from randomized trials are needed to improve the treatment of patients whose blood pressure remains high while they are receiving multiple agents. In such patients, the possible role of new drugs, such as inhibitors of renin and endothelin-1, requires evaluation.

SUMMARY AND RECOMMENDATIONS

The patient in the vignette has elevated blood pressure, despite taking three medications, with evidence of target-organ injury (retinal arteriopathy and left ventricular hypertrophy). Careful assessment of her adherence to therapy is warranted. Such adherence may be improved by addressing the reasons for nonadherence, such as side effects or the cost of medications, or by arranging for more frequent office visits or telephone contact.

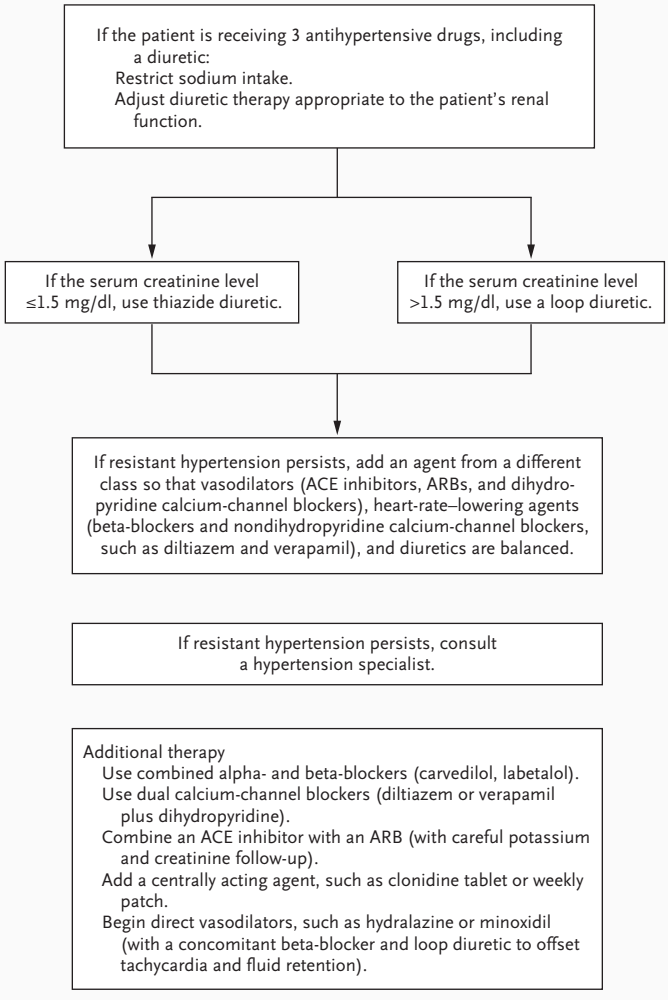

Figure 2. Optimization of Drug Therapy for Resistant Hypertension.
If resistant hypertension persists, patients can augment their therapy with an agent from a different class of drugs. For example, if the patient is receiving an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) plus a diuretic and a beta-blocker, a dihydropyridine calcium-channel blocker can be added. If the patient is receiving an ACE inhibitor or an ARB plus a diuretic and a dihydropyridine calcium-channel blocker, a beta-blocker can be added. The practitioner may consider adding an aldosterone antagonist to any of the combinations (but with extreme caution if the patient is receiving an ACE inhibitor or an ARB because of concern regarding hyperkalemia).

The ibuprofen she takes for osteoarthritis should probably be discontinued, since it may contribute to blood-pressure elevation, and be replaced with acetaminophen. Weight loss and a restriction of dietary sodium should be encouraged. Since volume overload is common in refractory hypertension, she could increase her dose of diuretic (with repletion of potassium as needed). If these inter-

ventions are ineffective, a different class of drug (e.g., a calcium-channel blocker) could be added, and the patient could be screened for renovascular hypertension, even though in patients with this condition, blood pressure may remain elevated despite intervention. Regular follow-up is warranted, with a goal of maintaining the blood pressure below 140/90 mm Hg.

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