

Treatment of resistant hypertension

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INTRODUCTION

— Resistant hypertension is defined as a blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses, one of which should be a diuretic (the diuretic should be selected based upon kidney function) [1-5]. The diagnosis of true resistant hypertension requires that white coat hypertension and nonadherence to treatments have both been excluded as reasons for the uncontrolled blood pressure (algorithm 1). Patients with blood pressures at goal while taking four or more antihypertensive medications are considered to have "controlled resistant hypertension."

Patients with resistant hypertension are at high risk for adverse cardiovascular events and are more likely to have a secondary cause of high blood pressure, which may be at least in part reversible. By definition they require more aggressive medication treatment, as well as the potential use of specialized interventions, to control their high blood pressure [1].

The treatment and prognosis of resistant hypertension that is not due to secondary causes will be reviewed here. The definition, epidemiology, risk factors, diagnosis, and evaluation of resistant hypertension, and secondary causes of hypertension, such as renovascular disease and primary aldosteronism, are discussed elsewhere:

- (See "[Definition, risk factors, and evaluation of resistant hypertension](#)".)

- (See "[Evaluation of secondary hypertension](#)".)

TREATMENT GOAL

— The goal blood pressure for patients with resistant hypertension is the same as that in hypertensive patients without treatment resistance ([table 1](#)) [6]. Goal blood pressure is discussed in detail elsewhere. (See "[Goal blood pressure in adults with hypertension](#)".)

MANAGEMENT

Identify and treat secondary causes

— An essential component of the management of resistant hypertension is identification and subsequent treatment of potentially reversible causes of secondary hypertension ([table 2](#)). The most common of these are obstructive sleep apnea (OSA), primary aldosteronism, and renal artery stenosis [7]. The possible presence of secondary rather than primary hypertension (formerly called "essential" hypertension) is suggested by a number of clinical clues, one of which is resistant hypertension. Thus, secondary hypertension should be considered in most patients with resistant hypertension:

- The evaluation for secondary hypertension in patients with resistant hypertension is presented elsewhere. (See "[Definition, risk factors, and](#)

evaluation of resistant hypertension", section on 'Secondary causes of hypertension' and "Definition, risk factors, and evaluation of resistant hypertension", section on 'Other components of evaluation'.)

- The clinical clues suggesting secondary hypertension are discussed in detail separately. (See "Evaluation of secondary hypertension".)

The management of secondary hypertension frequently differs from the treatment of primary hypertension and depends upon the specific disorder:

- Primary aldosteronism (see "Treatment of primary aldosteronism")
- Renovascular hypertension (see "Treatment of unilateral atherosclerotic renal artery stenosis" and "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney")
- Obstructive sleep apnea (OSA) (see "Management of obstructive sleep apnea in adults")
- Pheochromocytoma (see "Treatment of pheochromocytoma in adults")
- Cushing's syndrome (see "Overview of the treatment of Cushing's syndrome")
- Aortic coarctation (see "Management of coarctation of the aorta")
- Hyperparathyroidism or hypothyroidism (see "Primary hyperparathyroidism: Management" and "Treatment of primary hypothyroidism in adults")

Stop medications that raise blood pressure

— A variety of medications can raise the blood pressure and worsen underlying hypertension (table 3) [8,9]. Of these, nonsteroidal antiinflammatory drugs (NSAIDs) are probably the most common. (See "NSAIDs and acetaminophen: Effects on blood pressure and hypertension".)

Patients with resistant hypertension who are taking a medicine that can exacerbate hypertension should discontinue the medication (or have the dose reduced), provided that doing so would not be harmful.

Prescribe lifestyle modification

— Lifestyle modification (eg, weight loss, exercise, eating a healthy diet) has multiple health benefits and can also lower blood pressure ([figure 1](#)). (See ["Overview of hypertension in adults"](#), section on 'Nonpharmacologic therapy'.)

Few studies have evaluated the efficacy of lifestyle modification specifically in patients with resistant hypertension. However, several factors, in particular obesity and high sodium intake, are known to increase the risk for resistant hypertension [1]. As such, nonpharmacologic therapies are recommended to help control blood pressure and reduce the need for further medications in such patients. The main modalities include:

- Following the Dietary Approaches to Stop Hypertension (DASH) diet (see ["Diet in the treatment and prevention of hypertension"](#))
- Reducing sodium intake and increasing potassium intake (see ["Salt intake, salt restriction, and primary \(essential\) hypertension"](#) and ["Potassium and hypertension"](#))
- Losing weight (in obese and overweight patients) (see ["Overweight, obesity, and weight reduction in hypertension"](#))
- Exercising (see ["Exercise in the treatment and prevention of hypertension"](#))
- Moderating alcohol intake (if excessive) (see ["Cardiovascular benefits and risks of moderate alcohol consumption"](#), section on 'Hypertension')

It may be difficult for patients to achieving lasting lifestyle and dietary changes. Thus, professional guidance and follow-up with a certified dietitian or nutritionist should be provided, if available.

Address nonadherence to antihypertensive therapy

— Nonadherence to antihypertensive therapy is a major contributor to inadequate blood pressure control and is a common problem in patients who have apparent treatment resistance. (See "[Definition, risk factors, and evaluation of resistant hypertension](#)", section on 'Apparent, true, and pseudoresistant hypertension'.)

Regimens should be simplified, and long-acting combination agents should be used as much as possible in order to reduce the number of prescribed pills and to permit once-daily dosing. Treatment adherence worsens as the use of pills, complexity of the dosing regimen, and out-of-pocket costs increase. Medication-related adverse effects should be discussed, and side effects should be addressed, with down-titration of or substitution for the offending agent. Patients who have real or perceived side effects to many different antihypertensive drugs are often the most difficult to treat [10].

The assessment of adherence to antihypertensive therapy and strategies to improve adherence are presented in detail elsewhere ([table 4](#)). (See "[Patient adherence and the treatment of hypertension](#)", section on 'Assessment of adherence' and "[Patient adherence and the treatment of hypertension](#)", section on 'Methods to improve adherence'.)

Stepwise approach to pharmacologic therapy

— The following approach applies to patients with resistant hypertension who do not have a reversible secondary cause of hypertension ([figure 1](#)) [7].

Drug treatment may differ in patients with specific secondary causes. (See ['Identify and treat secondary causes'](#) above.)

By definition, patients with resistant hypertension are treated with at least three antihypertensive agents, including a diuretic (usually a thiazide, but loop diuretics are selected in patients with estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²). The specific regimen depends upon consideration of prior benefit, history of adverse events, financial limitations, and the presence of concomitant disease processes such as kidney disease and diabetes. Our general approach is to sequentially combine agents with different mechanisms of action. Specifically, the triple combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a long-acting dihydropyridine calcium channel blocker (usually [amlodipine](#)), and a long-acting thiazide-like diuretic is often effective and generally well tolerated [2,3]. In addition, in patients with uncontrolled blood pressure, medications should be provided at maximally tolerated doses and taken at the appropriate dosing frequency.

However, most patients with resistant hypertension are being treated with an alternative three-drug regimen (other than the one described above). In addition, most who are prescribed four or more antihypertensive drugs are not receiving a mineralocorticoid receptor antagonist [11].

Our approach outlined here discusses the treatment of patients with confirmed resistant hypertension. Confirmation of treatment resistance is provided in a separate topic ([algorithm 1](#)). (See ["Definition, risk factors, and evaluation of resistant hypertension"](#).)

Switch to a more potent diuretic (if necessary)

— In most patients with resistant hypertension, our initial approach is to treat with more potent diuretic therapy ([figure 1](#)):

- In patients who are taking a thiazide-type diuretic (eg, **hydrochlorothiazide**), and who have an $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$, we suggest switching to a thiazide-like diuretic (either **chlorthalidone** or **indapamide**). In patients with an $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$ who are already treated with a thiazide-like diuretic, and who have persistent signs of hypervolemia (ie, edema), we suggest adding a loop diuretic to the thiazide-like diuretic (ie, sequential nephron blockade).

We generally begin **chlorthalidone** at 12.5 mg daily, which requires splitting of the 25 mg pill, with subsequent titration up to 25 mg daily or, rarely, higher. If **indapamide** is used, we start at 1.25 mg daily, titrating up to 5 mg daily as needed. For patients already being treated with **hydrochlorothiazide**, we discontinue it and substitute chlorthalidone or indapamide.

- In patients with an $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, we suggest switching to a loop diuretic; if such patients are already taking a loop diuretic, then we intensify the loop diuretic dose, unless the patient develops signs of hypovolemia.

Furosemide and **bumetanide** are relatively short acting and usually require at least twice-daily dosing. A loop diuretic with a longer duration of action and more consistent absorption, such as **torsemide**, may be more effective.

Monitoring of serum electrolytes is necessary when diuretics are switched or when doses are changed. Hypokalemia is a more common problem in patients with resistant hypertension due at least in part to higher aldosterone levels, which explains the responsiveness of patients with resistant hypertension to mineralocorticoid receptor antagonists. (See '**Add a mineralocorticoid receptor antagonist (if necessary)**' below.)

Persistent volume expansion (whether or not it is sufficient to produce detectable peripheral edema) contributes to resistant hypertension, even among patients treated with conventional doses of thiazide-type diuretics. This was illustrated in a study of 279 patients with resistant hypertension, 85 percent of whom were being treated with a thiazide diuretic [12]. Serum brain-type natriuretic peptide and atrial natriuretic peptide levels were significantly higher among patients with resistant hypertension compared with controls, suggesting hypervolemia.

Effective diuretic use is almost always necessary to achieve blood pressure control in patients with resistant hypertension [13]. Diuretics should be titrated until the blood pressure goal is attained, the maximum recommended dose of the medication has been reached, or the patient develops signs suggestive of hypovolemia (eg, fatigue, orthostatic hypotension, or decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the serum creatinine concentration). If overdiuresis is suspected, diuretic therapy should be reduced.

In patients without severe renal impairment, the thiazide-like diuretics, including [chlorthalidone](#) and [indapamide](#), are preferred over [hydrochlorothiazide](#) for the treatment of resistant hypertension [14,15]. Chlorthalidone and indapamide have more potent antihypertensive effects than hydrochlorothiazide due, in part, to their longer half-lives. The supportive data are presented elsewhere. (See "[Choice of drug therapy in primary \(essential\) hypertension](#)", section on "[Thiazide-like versus thiazide-type diuretics](#)".)

Most studies that have compared [chlorthalidone](#) with [hydrochlorothiazide](#) have evaluated patients with mild to moderate hypertension. Limited data

suggest that chlorthalidone also provides comparatively greater benefit in patients with resistant hypertension [16].

Among patients with an eGFR of less than 30 mL/min/1.73 m², thiazide diuretics are less effective, and loop diuretics, such as furosemide, torsemide, or bumetanide, may be necessary for effective volume and blood pressure control. One option is to discontinue the thiazide-like diuretic and begin appropriate loop diuretic therapy in its place. However, it is not uniformly necessary to discontinue the thiazide-like diuretic. Adding a loop diuretic in combination with a thiazide-like diuretic (termed sequential nephron blockade) can be highly effective in patients with resistant hypertension and chronic kidney disease [17].

Add a mineralocorticoid receptor antagonist (if necessary)

— In patients with resistant hypertension and uncontrolled blood pressure despite potent diuretic therapy, we suggest adding a mineralocorticoid receptor antagonist (spironolactone or eplerenone) (figure 1). A potassium-sparing diuretic (eg, amiloride, triamterene) is an alternative if a mineralocorticoid receptor antagonist cannot be used.

We usually begin spironolactone at 12.5 mg once daily (which requires splitting of a 25 mg tablet) before titrating to 25 and, if necessary, 50 mg once daily. The risk of adverse effects such as gynecomastia, breast tenderness, and erectile dysfunction increases with higher doses. We generally do not increase the spironolactone dose above 50 mg once daily unless the patient has proven primary aldosteronism. The more specific aldosterone blocker, eplerenone, does not induce the side effects seen with spironolactone. However, eplerenone is less potent and often requires twice-daily dosing (at 50 to 100 mg) to be as effective for blood pressure lowering. An eplerenone dose of 50 mg once daily can be prescribed as initial trial,

with dose and frequency escalations undertaken as needed to achieve blood pressure control. [Amiloride](#) 5 to 10 mg/day may also be an effective alternative to spironolactone.

The serum potassium should be measured (usually in conjunction with measurement of other electrolytes and creatinine) two to four weeks after initiation or dose titration of a mineralocorticoid receptor antagonist. Measuring at two weeks, rather than waiting until four weeks, is appropriate in patients whose baseline serum potassium is at the upper end of the normal range, who are taking ACE inhibitors or ARBs, or with chronic kidney disease.

Patients who are being treated with mineralocorticoid receptor antagonists or potassium-sparing diuretics are at risk for the development of hyperkalemia [18]. The risk is increased among patients with chronic kidney disease and among those who are also treated with other drugs that can cause hyperkalemia, such as ACE inhibitors, ARBs, NSAIDs. (See "[Causes and evaluation of hyperkalemia in adults](#)".)

A variety of interventions can be used in patients with resistant hypertension who develop hyperkalemia but who require [spironolactone](#) for effective blood pressure control. Actions include lowering the dose of other offending medications (ACE inhibitors, ARBs), using loop diuretics, and prescribing gastrointestinal cation exchangers, which can permit patients with reduced kidney function to remain on mineralocorticoid receptor antagonists [19]. The treatment and prevention of hyperkalemia in such patients is presented elsewhere. (See "[Treatment and prevention of hyperkalemia in adults](#)", section on 'Patients who can have the serum potassium lowered slowly'.)

[Spironolactone](#), [eplerenone](#), and [amiloride](#) provide significant antihypertensive benefit when added to existing multiple-drug regimens in

patients with resistant hypertension [20-26]. This effect may reflect, at least in part, significantly higher plasma aldosterone levels in patients with resistant hypertension compared with individuals who have normal blood pressure or controlled hypertension on one or two medications [12]. However, spironolactone, which has been most widely studied, can also lower the blood pressure in patients with resistant hypertension who have normal plasma and urine aldosterone levels [25].

The effect of spironolactone in patients with resistant hypertension has been evaluated in multiple randomized trials, each of which found that it was more effective than placebo or other antihypertensive drugs [17,22,24,27-29]. The most compelling data come from the PATHWAY-2 trial, a randomized, double-blind crossover study comparing spironolactone (25 to 50 mg/day) with placebo, doxazosin, or bisoprolol in 285 patients with resistant hypertension (mean clinic blood pressure 157/90 mmHg and mean home blood pressure 148/84 mmHg despite therapy with an ACE inhibitor or ARB, a calcium channel blocker, and a diuretic) [27]. Spironolactone significantly reduced mean home systolic pressure at 12 weeks by nearly 9 mmHg compared with placebo and by between 4 to 5 mmHg compared with doxazosin and bisoprolol. The superiority of spironolactone did not depend upon the plasma renin activity. Hyperkalemia developed in 2 percent of patients taking spironolactone; the frequency of serious adverse events and withdrawal of therapy due to adverse events was similar with each antihypertensive drug.

The antihypertensive effect of spironolactone was evaluated in a post-hoc observational analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which included 1411 patients whose blood pressure was not controlled on three antihypertensive drugs (mean blood pressure 157/85 mmHg) [21]. The mean baseline serum potassium was 4.2 mEq/L, and the

mean serum creatinine was 1.1 mg/dL (99 micromol/L). The addition of spironolactone (median dose 25 mg/daily) as a fourth drug was associated with a mean 22/10 mmHg reduction in blood pressure at one-year follow-up. The mean rise in serum potassium was 0.4 mEq/L, with hyperkalemia (serum potassium >5.5 mEq/L) occurring in 4 percent.

In a substudy of the PATHWAY-2 trial described above, [amiloride](#) 10 mg once daily was equally effective in lowering clinic blood pressure, compared with [spironolactone](#) 25 once daily. These findings illustrate that amiloride may be an effective alternative as the fourth-line medication in resistant hypertension.

Additional drugs (if necessary)

— Some patients remain hypertensive despite taking a four-drug regimen that ideally includes a thiazide-like diuretic, such as [chlorthalidone](#), and a mineralocorticoid receptor antagonist, such as [spironolactone](#). There is little evidence to help guide the choice of a fifth antihypertensive medication in such patients.

Patient factors (eg, preferences, side effects) and other characteristics can help guide choices ([figure 1](#)). As an example, those with faster heart rates (eg, >70 beats per minute) may benefit from next adding a beta blocker. A vasodilating beta blocker, such as [labetalol](#), [carvedilol](#), or [nebivolol](#) may provide more antihypertensive benefit with fewer side effects compared with traditional beta blockers, particularly when high doses are used (although head-to-head, full-dose comparisons are lacking) [[30](#)].

Centrally acting agents that lower sympathetic activity may also be effective, but adverse effects are more common (eg, somnolence, dry mouth), and high-quality data to support their use are lacking. Potential choices include [clonidine](#) (taken two to three times per day orally or applied as a dermal

patch formulation changed weekly) or **guanfacine**. Guanfacine may be preferable to clonidine because it can be dosed once daily at bedtime.

Other medication options include alpha-1 antagonists such as **doxazosin** or direct vasodilators (**hydralazine** or **minoxidil**). The direct vasodilators hydralazine and minoxidil are generally reserved for patients who remain hypertensive despite trying the other approaches previously listed. Fluid retention and tachycardia are common side effects, and loop diuretics are often needed to control hypervolemia. Minoxidil also causes hirsutism, which may be a particular problem in women.

Multidisciplinary team approach

— There is evidence that a team approach in the comprehensive care of hypertension patients can help improve the control of high blood pressure [31-33]. This can potentially involve coordinated care and assistance from a variety of team members such as clinician specialists (eg, endocrinologists, nephrologists, cardiologists) along with nurses, physician assistants, pharmacists, community health workers, dieticians, social workers, and psychologists. There are few studies specifically in resistant hypertension; however, the evidence that a team approach is effective among patients with hypertension in general is growing. The merits of this strategy likely also apply to resistant hypertension, given the complex and often multifactorial etiology of inadequate blood pressure control in this population.

In addition, involving patients in monitoring their own blood pressure at home may also improve control [34]. Out-of-office monitoring can be especially effective to reduce blood pressure when undertaken in conjunction with other strategies to control hypertension (eg, telemedicine, multidisciplinary teams).

When to refer

— Referral to a hypertension specialist is appropriate for the following patients [1,35]:

- If a specific secondary cause of hypertension is suspected
- If the blood pressure remains elevated despite six months of intensive treatment with at least three drugs from those described above (see 'Stepwise approach to pharmacologic therapy' above)

In the United States, the American Hypertension Specialist Certification Program provides a [list of certified specialists](#). The American Heart Association certifies and provides a list of accredited Comprehensive Hypertension Centers and Hypertension Practice Centers for referrals.

EXPERIMENTAL THERAPIES

— Multiple experimental therapies have been evaluated for resistant hypertension including novel medications [36], renal denervation techniques, and electrical stimulation of the carotid sinus baroreceptors.

Several other procedures, including the creation of an arteriovenous anastomosis [37,38], have been tested in patients with resistant hypertension, although development of such techniques has been abandoned.

Renal denervation

— Preliminary data suggest that denervation of the renal sympathetic nerves (also known as renal nerve denervation), either by catheter-based radiofrequency ablation or by catheter-based ultrasound ablation, reduces blood pressure in patients without resistant hypertension [39-42]. The

effectiveness of renal nerve denervation has not yet been established in patients with resistant hypertension [43-45].

Three sham-controlled trials demonstrated modest short-term effects of renal nerve denervation on 24-hour ambulatory blood pressure in patients **not** taking antihypertensive medication (reductions of 4/3 mmHg, 4/2 mmHg, and 5/4 mmHg at two to three months, compared with a sham procedure) [40-42]. The preliminary findings of a third trial in patients with treated hypertension (but **not** resistant hypertension) showed a six-month reduction in 24-hour ambulatory blood pressure of 7/4 mmHg compared with sham denervation [39].

In patients with resistant hypertension, the best data come from a large, blinded, randomized trial (SYMPPLICITY HTN-3) that failed to demonstrate benefit from renal nerve denervation compared with a sham procedure [43,44]. In SYMPPLICITY HTN-3, 535 patients with treatment-resistant hypertension (systolic pressure >160 mmHg despite three or more antihypertensive medications, including a diuretic) were assigned to renal nerve denervation or a sham procedure; blood pressure decreased to a similar degree in both groups at six months, and there was no difference in the incidence of serious adverse events.

Several other trials reached conclusions similar to SYMPPLICITY HTN-3 [46-48]. As an example, the open-label SYMPATHY trial randomly assigned 139 patients with resistant hypertension to routine care or routine care plus renal nerve denervation [46]. At six months, 24-hour ambulatory systolic pressure decreased more in the control group than in the denervation group (a decline of 6.6 versus 5.6 mmHg), although this was not statistically significant.

In contrast to SYMPPLICITY HTN-3, the results of several unblinded studies suggested that renal nerve denervation could substantially lower blood pressure in patients with resistant hypertension [49-60]. As an example, an open-label randomized trial (Renal Denervation for Hypertension [DENERHTN]) compared stepped antihypertensive therapy alone with stepped antihypertensive therapy plus renal denervation in 106 patients with confirmed resistant hypertension despite therapy with **indapamide**, **amlodipine**, and **ramipril** (or **irbesartan** if allergic to ACE inhibitors) [49]. Stepped antihypertensive therapy consisted of **spironolactone**, **bisoprolol**, **prazosin**, and rilmenidine added (in that order) at monthly intervals if home blood pressure remained above 135/85 mmHg. At six months, the change in 24-hour ambulatory systolic pressure decreased significantly more in the denervation group (-15.4 versus -9.5 mmHg). However, this study had several limitations. In addition to the lack of a sham intervention, all patients lost to follow-up were in the denervation group and were not analyzed, the number of antihypertensive medications used at six months was similar in both groups, and the baseline blood pressure was higher in the denervation group, suggesting that the results could be due in part to regression to the mean. A smaller trial found that spironolactone lowered 24-hour ambulatory systolic pressure more than renal nerve denervation [61].

Stimulation of carotid sinus baroreceptors

— Stimulation of the carotid sinus baroreflex system, or baroreflex activation therapy (BAT), may decrease blood pressure in patients with resistant hypertension. Feasibility studies have shown reductions in blood pressure after implantation of different devices designed to stimulate the carotid baroreflex system [62-66]. As with renal denervation, BAT is not approved for treatment of hypertension in the United States [67].

In the Rheos Pivotal Trial, 265 patients with resistant hypertension (defined as a mean office blood pressure, based upon five readings, greater than 160/80 mmHg and a mean 24-hour ambulatory systolic blood pressure greater than or equal to 135 mmHg despite at least three antihypertensive medications including a diuretic) underwent surgical implantation of a device designed to stimulate the carotid baroreceptors [68]. One month after surgery, patients were randomly assigned to have BAT turned on immediately or to have BAT turned on six months later. The patients were followed for at least 12 months.

The major findings from this trial were as follows:

- At six months, patients receiving BAT had a nonsignificantly larger decrease in systolic pressure (16 versus 9 mmHg) and a nonsignificantly greater likelihood of having a 10 mmHg or larger decrease in systolic pressure (54 versus 46 percent). In addition, patients receiving BAT were significantly more likely to achieve a goal systolic pressure of 140 mmHg or lower (42 versus 24 percent).
- At 12 months, the mean reduction in systolic pressure in the BAT group was 25 mmHg; more than 80 percent of these patients had at least a 10 mmHg decrease in systolic pressure.
- Within one month of surgery, 35 percent of patients had a serious procedure-related adverse event, including nerve injury. In most patients, procedure-related adverse events resolved spontaneously. Seven patients died (3 percent), but none of the deaths were attributable to the device.

After the 12-month trial phase ended, open-label follow-up continued for an average of 28 months [69]; the antihypertensive effects of the device persisted, and there were no device-associated deaths.

Because the Rheos Pivotal Trial failed in two of its five primary endpoints, it was not approved by the US Food and Drug Administration (FDA) for the indication of resistant hypertension in the United States; the device was therefore discontinued.

A second BAT device, which is inserted into the carotid sinus by endovascular deployment (rather than surgical implantation), lowered 24-hour ambulatory blood pressure at six months by 21/12 mmHg in 30 patients with apparent resistant hypertension [66]. Serious adverse events occurred in four patients (13 percent).

PROGNOSIS

— Patients with resistant hypertension are more likely to have target-organ damage and are at greater risk of stroke, myocardial infarction, heart failure, and/or chronic kidney disease compared with patients who have more easily controlled hypertension [70-74]. The high cardiovascular risk is attributable in part to long-standing, poorly controlled hypertension [75] and to the coexistence of other cardiovascular risk factors, including left ventricular hypertrophy, obesity, diabetes, hyperlipidemia, chronic kidney disease, and obstructive sleep apnea (OSA).

SOCIETY GUIDELINE LINKS

— Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Hypertension in adults](#)".)

INFORMATION FOR PATIENTS

— UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see ["Patient education: High blood pressure in adults \(Beyond the Basics\)"](#) and ["Patient education: High blood pressure treatment in adults \(Beyond the Basics\)"](#) and ["Patient education: High blood pressure, diet, and weight \(Beyond the Basics\)"](#))

SUMMARY AND RECOMMENDATIONS

- Resistant hypertension is defined as a blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses, one of which should be a diuretic. The diagnosis of true resistant hypertension requires that white coat hypertension and nonadherence to treatments have both been excluded as reasons for the uncontrolled blood pressure ([algorithm 1](#)). Patients with blood pressures at goal while taking four or more

antihypertensive medications are considered to have "controlled resistant hypertension." (See ['Introduction'](#) above.)

- The goal blood pressure for patients with resistant hypertension is the same as that in hypertensive patients without treatment resistance ([table 1](#)). (See ['Treatment goal'](#) above.)
- An essential component of the management of resistant hypertension is identification and subsequent treatment of potentially reversible causes of secondary hypertension ([table 2](#)). The most common of these are obstructive sleep apnea (OSA), primary aldosteronism, and renal artery stenosis. The possible presence of secondary rather than primary hypertension is suggested by a number of clinical clues, one of which is resistant hypertension. Thus, secondary hypertension should be considered in most patients with resistant hypertension. (See ['Identify and treat secondary causes'](#) above.)

In addition, a variety of medications can raise the blood pressure and worsen underlying hypertension ([table 3](#)); such medications should be stopped, provided that doing so would not be harmful. (See ['Stop medications that raise blood pressure'](#) above.)

- Lifestyle modification (eg, weight loss, exercise, eating a healthy diet) has multiple health benefits and can also lower blood pressure. As such, nonpharmacologic therapies are recommended to help control blood pressure and reduce the need for further medications in patients with resistant hypertension. (See ['Prescribe lifestyle modification'](#) above.)
- Nonadherence to antihypertensive therapy is a major contributor to inadequate blood pressure control and should be addressed. Regimens should be simplified, and long-acting combination agents should be used as much as possible in order to reduce the number of prescribed pills and

to permit once-daily dosing. Medication-related adverse effects should be discussed, and side effects should be addressed, with down-titration of or substitution for the offending agent. (See '[Address nonadherence to antihypertensive therapy](#)' above.)

●The following **stepwise approach** to pharmacologic therapy applies to patients with **confirmed** resistant hypertension who do not have a reversible secondary cause of hypertension (since drug treatment may differ in patients with specific secondary causes) ([figure 1](#)) (see '[Stepwise approach to pharmacologic therapy](#)' above):

- In patients who are taking a thiazide-type diuretic (eg, [hydrochlorothiazide](#)), and who have an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m², we suggest switching to a thiazide-like diuretic (either [chlorthalidone](#) or [indapamide](#)) (**Grade 2B**). In patients with an eGFR ≥ 30 mL/min/1.73 m² who are already treated with a thiazide-like diuretic, and who have persistent signs of hypervolemia (ie, edema), we suggest adding a loop diuretic to the thiazide-like diuretic (ie, sequential nephron blockade) (**Grade 2C**). However, in patients with an eGFR < 30 mL/min/1.73 m², we suggest switching to a loop diuretic (**Grade 2C**); if such patients are already taking a loop diuretic, then we intensify the loop diuretic dose, unless the patient develops signs of hypovolemia. (See '[Switch to a more potent diuretic \(if necessary\)](#)' above.)
- In patients with resistant hypertension and uncontrolled blood pressure despite potent diuretic therapy, we suggest adding a mineralocorticoid receptor antagonist ([spironolactone](#) or [eplerenone](#)) (**Grade 2B**). A potassium-sparing diuretic (eg, [amiloride](#), [triamterene](#)) is an alternative if a mineralocorticoid receptor antagonist cannot be

used. (See 'Add a mineralocorticoid receptor antagonist (if necessary)' above.)

- Some patients remain hypertensive despite taking a four-drug regimen that ideally includes a thiazide-like diuretic, such as [chlorthalidone](#), and a mineralocorticoid receptor antagonist, such as [spironolactone](#). Patient factors (eg, preferences, side effects) and other characteristics can help guide choices. As an example, those with faster heart rates (eg, >70 beats per minute) may benefit from next adding a beta blocker. Centrally acting agents that lower sympathetic activity may also be effective, but adverse effects are more common. Other options include alpha-1 antagonists such as [doxazosin](#) or direct vasodilators ([hydralazine](#) or [minoxidil](#)). The direct vasodilators hydralazine and minoxidil are generally reserved for patients who remain hypertensive despite trying the other approaches previously listed. (See 'Additional drugs (if necessary)' above.)

- Referral to a hypertension specialist is appropriate for the following patients: if a specific secondary cause of hypertension is suspected or if the blood pressure remains elevated despite six months of intensive treatment with at least three drugs from those described above. (See 'When to refer' above.)

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