Evaluation and Management of Resistant Hypertension: Core Curriculum 2024

Jennifer L. Cluett and Jeffrey H. William

Resistant hypertension is defined as blood pressure above goal despite confirmed adherence to 3 first-line antihypertensive agents or when blood pressure is controlled with 4 or more medications at maximal or maximally tolerated doses. In addition to meeting these criteria, identifying patients with true resistant hypertension requires both accurate in-office blood pressure measurement as well as excluding white coat effects through out-of-office blood pressure measurements. Patients with resistant hypertension are at higher risk for adverse cardiovascular events and are more likely to have a potentially treatable secondary cause contributing to their hypertension. Effective treatment of resistant hypertension includes ongoing lifestyle modifications and collaboration with patients to detect and address barriers to optimal medication adherence. Pharmacologic treatment should prioritize optimizing first-line, once daily, longer acting medications followed by the stepwise addition of second-, third-, and fourth-line agents as tolerated. Physicians should systematically evaluate for and address any underlying secondary causes. A coordinated, multidisciplinary team approach including clinicians with experience in treating resistant hypertension is essential. New treatment options, including both pharmacologic and device-based therapies, have recently been approved, and more are in the pipeline; their optimal role in the management of resistant hypertension is an area of ongoing research.

Complete author and article information provided at end of article.

Correspondence to J.H. William (jhwillia@bidmc.harvard.edu)

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Hypertension is the most common modifiable cardiovascular risk factor and is both a cause and a consequence of chronic kidney disease (CKD). Nearly half of adults in the United States have hypertension as defined as a systolic blood pressure (BP) ≥ 130 mm Hg and/or a diastolic BP ≥ 80 mm Hg. Patients whose BP is not at goal despite the use of 3 different classes of antihypertensive medications at the highest (or highest tolerated) doses are considered to have resistant hypertension (RHTN). Moreover, patients who require 4 or more BP medications to achieve BP control are categorized as having "controlled RHTN."

The true prevalence of RHTN is difficult to ascertain because many patients with uncontrolled hypertension are on suboptimal treatment regimens, have intermittent adherence, or have white coat effects. Patients whose BP is above goal despite treatment with multiple medications are more likely to have an underlying secondary cause of their hypertension, which may be reversible, at least in part, if it is found and treated. Moreover, patients with RHTN are nearly 50% more likely to have a cardiovascular event and 25% more likely to develop kidney failure than those with HTN that is not resistant.

Identifying patients with true RHTN and instituting appropriate evaluation and treatment strategies is critical to help them achieve their goal BP, to address underlying comorbid conditions, and to monitor for and treat target organ damage. Of note, both the definition of hypertension and treatment targets have evolved in the past decade after the publication of landmark clinical trials such as SPRINT and STEP. Different professional societies as well as national and international guideline organizations endorse different recommended thresholds for optimal BP control (Table 1).

In this installment of *AJKD*'s Core Curriculum we discuss how to identify, evaluate, and treat patients with RHTN. As seen in Figure 1, we will cover the importance of accurate BP measurement, medication adherence, lifestyle modifications that impact BP, and evaluations for secondary causes, and we will summarize the latest guideline recommendations for pharmacologic treatment strategies. We will also briefly discuss renal denervation (RDN), which was approved in November 2023 by the US Food and Drug Administration (FDA) for the treatment of uncontrolled hypertension in patients whose blood pressure is not at goal despite lifestyle modifications and medication therapy.

Additional Readings

- Acelajado MC, Hughes ZH, Oparil S, Calhoun DA. Treatment of resistant and refractory hypertension. *Circ Res*. 2019;124(7):1061-1070. doi:10.1161/circresaha.118.312156
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Table 1. Summary of Blood Pressure Target Recommendations

		Recommended BP Targets					
		2017 ACC/AHA	2020 ISH	2021 KDIGO	2021 AHA/ASA	2023 ESH	2024 ADA
Age	<65		120/70-130/80			<130/80	
	65-79		<140/90			<140/80	
	≥80		<140/90			140-150 SBP	
ASCVD risk	ASCVD risk <10%	<140/90					
	Clinical CVD/ASCVD risk ≥10%	<130/80					
Comorbidities	Diabetes						<130/80
	CKD (nondialysis)	<130/80		<120 SBP		<140/90	
	Kidney transplant recipient			<130/80			
	Stroke/TIA				<130/80		

Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESH, European Society of Hypertension; ISH, International Society of Hypertension; KDIGO, Kidney Disease Improving Global Outcomes; SBP, systolic blood pressure; TIA, transient ischemic attack.

➢ Carey RM, Calhoun DA, Bakris GL, et al; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72(5):e53-e90. doi:10.1161/HYP.0000000000000084

Figure 1. Framework and strategies for resistant hypertension clinic visit.

➢ Fay KS, Cohen DL. Resistant hypertension in people with CKD: a review. *Am J Kidney Dis*. 2021;77(1):110-121. doi:10.1053/j.ajkd.2020.04.017
➢ Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065

Factors to Consider at Every Visit

Case 1: *A 56-year-old woman is referred for uncontrolled BP. Her other past medical history includes hyperlipidemia and obesity. Her antihypertension regimen includes amlodipine 10 mg once daily, valsartan 320 mg once daily, and chlorthalidone 25 mg once daily. Her physical examination is notable for a BP of 151/76 mm Hg and a body mass index (BMI) of 34.8 kg/m^2.*

Question 1: Which of the following options could be used to evaluate for white coat effects *and* guide ongoing medication titration?

(a) Repeated auscultatory BP measurement by a physician at the end of a visit
(b) Automated office blood pressure monitoring (AOBP) performed in a quiet room
(c) 24-hour ambulatory blood pressure monitoring (ABPM)
(d) Self-measured blood pressure (SMBP) readings taken at home with proper technique

For the answer to this question, see the following text.

The first step in identifying patients with true RHTN should include confirming that their BP is above goal using optimal techniques for office-based BP readings, ideally by using AOBP. Then, if needed, white coat effect should be excluded by obtaining out-of-office BP readings either through SMBP readings or, where available, 24-hour ABPM. The term "white coat effect" applies to individuals on pharmacologic treatment for hypertension whose in-office BP readings average above 130/80 mm Hg while their out-of-office readings are consistently below 130/80. In case 1, the correct answer is (d): SMBP is the method that would both help discern the contribution of white coat effect as well as titrate antihypertensive medication dosing over time.

Optimal Office-based BP Measurement

The accuracy of BP measurements relies on both adequate patient preparation and proper technique. Key features for patient preparation are listed in Table 2. It is important to note that most of the potential errors in preparation will result in a BP reading that is higher rather than lower; the exception to this rule is using a BP cuff that is too large for the patient's arm size.

Table 2. Potential SBP Impacts for the Recommended Steps in Patient Preparation

Preparatory Step	Potential Impact on SBP
Empty bladder if needed	10 mm Hg
Place cuff on bare arm	5-50 mm Hg
Select proper cuff size	2-10 mm Hg
Arm supported with cuff at heart level	10 mm Hg
Back and feet supported	6 mm Hg
Legs uncrossed	2-8 mm Hg
Quiet space	10 mm Hg

Abbreviation: SBP, systolic blood pressure.

Auscultatory Versus Oscillometric BP Measurement

Traditionally, BP measurement required using a stethoscope placed over the brachial artery to auscultate Korotkoff sounds while simultaneously deflating a BP cuff connected to a mercury sphygmomanometer. Starting in 1998, mercury-based devices have been phased out of all US hospitals and clinics, replaced by aneroid devices which, although safer from an environmental and toxicology perspective, are delicate devices that are highly susceptible to error and require frequent calibration to ensure accuracy.

There are multiple sources of potential inaccuracy with auscultatory BP measurement including terminal digit bias and cuff-deflation errors, which can occur if the cuff pressure is released too quickly or too slowly. Newer oscillometric devices are now available that estimate BP during cuff deflation or inflation based on pulse wave amplitude and proprietary internal algorithms to compute systolic and diastolic BP. Though these devices are safer, do not require recalibration, and eliminate some potential sources of operator error common in manual BP measurement, they require independent validation to ensure accuracy.

Proper patient preparation is of paramount importance regardless of the method used for BP measurement. In most clinical scenarios, single manual auscultatory BP readings performed by physicians are likely to be less accurate than other methods of BP assessment.

Automated Office BP Measurement (AOBP)

AOBP refers to the use of a fully automated oscillometric BP device that can be programmed to take multiple BP readings after varying periods of rest with a single activation. It has the advantage of being able to be performed while the patient rests quietly and undisturbed, and can eliminate some important sources of operator bias and error. AOBP can be considered a reasonable surrogate for the average awake BP as measured with 24-hour ABPM and mitigates some, though not all, of the white coat effects seen when measuring BP in medical office settings. Further, AOBP has been used in many of the clinical trials that have informed guideline recommendations for BP targets such as SPRINT and ACCORD and has been shown

to have a strong correlation with target organ damage such as left ventricular mass index. As such, many guidelines recommend using AOBP, if available, as the preferred method of office-based BP measurement. In summary, AOBP can be used to minimize many of the common errors in office-based BP measurement; however, if the BP is still above goal on AOBP, an out-of-office BP strategy should be used next to confirm the diagnosis of RHTN.

Out-of-Office BP Measurement: 24-Hour ABPM and SMBP

Historically, clinical decision making for hypertension treatment has been based on BP readings assessed in medical offices, despite the recognition that office-based BPs are subject to myriad potential errors as previously detailed. For this reason, in 2015, the US Preventive Services Task Force began to recommend using out-of-office blood pressure measurements for diagnostic confirmation before starting treatment (Grade A recommendation). Subsequently, in 2017 the ACC/AHA guideline for the prevention, detection, evaluation and management of high blood pressure in adults took this one step farther by recommending out-of-office BP measurements not only to confirm the diagnosis of hypertension but also for titration of BP-lowering medication (Class of Recommendation 1, Level of Evidence A[SR]).

The 24-hour ABPM has long been considered the gold standard for BP measurement and has a unique advantage of being able to assess multiple readings during usual daytime activities in addition to collecting overnight assessments while sleeping. Moreover, ABPM has a stronger association with cardiovascular outcomes than other methods of BP assessment. ABPM also allows for the identification of different nocturnal BP patterns such as "nondipping," in which BP fails to drop by the expected 10%-20% while sleeping, or "reverse dipping," in which BP *increases* while sleeping. The availability of ABPM in the United States is variable, likely related to low or no reimbursement and the high relative cost of devices, both of which contribute to a paucity of clinicians with expertise in interpretation. Also, 24-hour ABPM can be challenging for some patients to perform because it can be disruptive to work and sleep schedules and may cause bruising or discomfort. For all these reasons, if out-of-office readings are needed for ongoing medication titration, SMBP is the preferred strategy.

There has been a relative explosion of interest in SMBP, particularly since the COVID-19 pandemic during which there was tremendous enthusiasm for health care solutions that could be implemented safely at home. High-quality SMBP requires patient education around many of the same features described earlier for proper preparation and technique that are needed in the office setting. National and international guidelines have been developed to provide standardized protocols for assessing BP outside the clinic setting; most of these show remarkable similarities and share some key themes, as listed in Table 3. Important features common among these guidelines are the instruction to check BP at standard times of the day in relation to the timing of BP medications and to use an average of at least 3 days of BP readings.

Table 3. Summary of Common Features Among Guidelines for Home BP Monitoring

Element	Comments
Frequency of BP readings	At least 2, measured 30-60 seconds apart
Time of day	AM before medications and eating PM before medications, either before dinner or before bedtime
Minimum readings if BP uncontrolled	At least 12 readings over 3-7 days Some suggest discarding first day
Goal	Average BP <130/<80
Type of device	Validated upper arm oscillometric device preferred Wrist devices only in settings of large arm circumferences

Abbreviation: BP, blood pressure.

Patient education on proper steps for guideline-based SMBP can reduce much of the perceived lability in readings by ensuring that BP is measured with proper position and technique. Using a 3-7 day average further distills the BP into a single reading that is simpler to use for clinical decision making. Although technology features such as direct transmission into an electronic health record and/or Bluetooth connectivity can eliminate some potential issues (such as inaccurate or selective reporting of readings), they are not necessary. High-quality, guideline-based SMBP can be done with relatively inexpensive BP monitors and does not require potentially costly technology solutions, high levels of digital literacy, or internet access, though an accurate BP monitor is critical.

Several online resources list BP devices that have been validated and reviewed by a group of independent experts in the field to ensure accuracy (including www.validatebp.org and www.stridebp.org). There are also numerous online videos for patients to view through the US Department of Veterans Affairs and the American Medical Association, to name a few. Finally, SMBP is a valuable tool to increase patient engagement and adherence when paired with timely clinical review and feedback.

Additional Readings

- Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension*. 2019;73(5):e35-e66. doi:10.1161/hyp.0000000000000087 ★ESSENTIAL READING
- Roerecke M, Kaczorowski J, Myers MG. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179(3):351-362. doi:10.1001/jamainternmed.2018.6551

➢ Shimbo D, Artinian NT, Basile JN, et al; American Heart Association and the American Medical Association. Self-measured blood pressure monitoring at home: a joint policy statement from the American Heart Association and American Medical Association. *Circulation*. 2020;142(4):e42-e63. doi:10.1161/CIR.0000000000000803

Medication and Other Substance-related Hypertension

Case 2: *A 73-year-old woman with hypertension, hyperlipidemia, obesity, obstructive sleep apnea (OSA), and gastroesophageal reflux presents to her primary care physician for routine follow-up evaluation. She has been seeing an orthopedic surgeon and plans to have a total knee replacement in the next 2 months. She is currently taking losartan 50 mg twice daily, amlodipine 5 mg daily, hydrochlorothiazide 12.5 mg daily, carvedilol 6.25 mg twice daily, and rosuvastatin 5 mg. In addition, she has been using over-the-counter naproxen 220 mg twice daily for her knee pain. On examination, her BP is 148/91 mm Hg and BMI is 33.6 kg/m^2. At the most recent visit 6 months ago, her BP was 131/76 mm Hg.*

Question 2: Which of the following pharmacologic strategies is the most appropriate next step?

(a) Increase losartan from 50 mg twice daily to 100 mg twice daily.
(b) Change amlodipine from 5 mg once daily to verapamil extended release 180 mg once daily.
(c) Switch naproxen 220 mg to topical diclofenac gel.
(d) Add spironolactone 25 mg once daily.

For the answer to this question, see the following text.

Many medications, both prescribed and over the counter, can cause increased BP. Examples include calcineurin inhibitors, methylphenidate, vascular endothelial growth factor (VEGF) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Other non-medication substances such as alcohol, cocaine, caffeine, tobacco, amphetamines, herbal supplements, or even licorice are frequently cited as contributors to elevated BP. In addition to directly increasing BP, either temporarily or longer term, some of these substances, such as NSAIDs, can antagonize prescribed antihypertensive medications, making their impact on BP particularly problematic.

Because patients either may not be aware of these potential impacts on BP or they be reluctant to discuss them, such as in the case of recreational drug use, they may not spontaneously report the use of them. Clinicians should routinely ask about the use of medications or other substances that increase BP and employ strategies to either minimize their use or switch to alternatives without similar impacts, which makes the correct answer (c).

Additional Reading

➢ Foy MC, Vaishnav J, Sperati CJ. Drug-induced hypertension. *Endocrinol Metab Clin North Am*. 2019;48(4):859-873. doi:10.1016/j.ecl.2019.08.013

Adherence to Antihypertensive Medications

Case 3: *A 43-year-old woman with a past medical history of pre-eclampsia and postpartum hypertension is seen in a follow-up visit. Two years after delivery, her BP has remained elevated. Her current regimen is labetalol 200 mg twice daily, and hydrochlorothiazide 25 mg once daily. Lisinopril 10 mg once daily in the evening was added a few months ago. Her BP in the office is 148/91 mm Hg, as determined by AOBP. She acknowledges that she often forgets to take her evening doses of labetalol and lisinopril.*

Question 3: Which of the following strategies would be the most effective way to improve medication adherence?

(a) Ask her to bring all of her pill bottles to each visit for review.
(b) Change medications to long-acting medications dosed once daily where possible.
(c) Check urine or serum metabolites of prescribed antihypertensives.
(d) Instruct the medical assistant to perform a medication reconciliation at the start of each visit.

For the answer to this question, see the following text.

Despite the importance of medication adherence to achieving BP, over half of patients do not take their medications as prescribed. In fact, nearly 25% never fill their initial prescription. Nonadherence increases with increased pill burden; half of the patients who are prescribed at least 5 medications are nonadherent.

There is no gold standard to assess medication adherence. The available techniques are either inaccurate, such as clinician impression or patient self-report, or are too costly for routine clinical use, as with measurement of serum or urine metabolites of antihypertensive medications. Long-acting medications that can be dosed once a day are preferred when available and low cost, such as switching the shorter-acting twice daily carvedilol to the extended-release carvedilol phosphate as in question 3, so the correct answer is (b). When feasible, antihypertensive regimens should be consolidated into combination pills so that the patient can take the fewest number of pills each day.

Newly diagnosed or chronic comorbid conditions can increase the likelihood of nonadherence, as does overall complexity of the medication regimen. Further, as medications and circumstances change, patients who were previously adherent to their medications may no longer take them consistently or at all, as might be the case for a patient whose antihypertensive medications were held

during an inpatient admission and were never resumed after discharge.

Unlike some other chronic medical conditions in which pharmacologic treatment is associated with symptomatic improvement, hypertension is essentially asymptomatic for most patients. Thus, any unpleasant side effects are particularly problematic because they are not offset by any immediate perceived benefit in health. As such, medication side effects should also be routinely assessed and, where possible, addressed. Many side effects from antihypertensive medications are dose-related, such as the lower extremity edema often seen with higher doses of dihydropyridine calcium channel blockers (CCB) that can be reduced or eliminated by using a lower dose.

As mentioned previously, some promising studies have shown that using SMBP, particularly when paired with timely feedback and co-interventions, can be a useful patient engagement tool and may have a positive impact on medication adherence.

Nonadherence can be multifactorial, and addressing it can be challenging; Table 4 lists some common barriers to adherence and some strategies to minimize them. Clinicians should routinely ask about barriers to medication adherence at every clinical encounter using nonjudgmental language and should actively seek to minimize any barriers.

Table 4. Strategies to Minimize or Address Common Barriers to Medication Adherence

Barriers to Medication Adherence	Strategies to Minimize/Address
Cost	• Choose low-cost generic medications where feasible • Reduce copays with combination tablets (if generic)
Complexity of regimen/ too many pills	• Convert to once daily formulations where available • Convert to combination tablets to minimize pill burden • Use blister packs/pill boxes • Minimize trips to pharmacy for refills • Use 90-day refills instead of 30-day refills • Ensure all medications (not just BP medications) are eligible to be refilled at the same time • Use mail order if available/cost effective
Adverse effects of medications	• Use lowest effective doses of BP medications to minimize side effects • ARB/ACE inhibitors can counteract edema from CCBs • ARB/ACE inhibitors can counteract hypokalemia from thiazides
Patient motivation/ insight	• Multidisciplinary team-based care • Patient education and motivational interviewing • Text messaging reminders • Home BP monitoring with ongoing feedback through electronic health record and ability to modify medications and doses

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

Additional Reading

➢ Izeogu C, Kalinowski J, Schoenthaler A. Strategies to improve adherence to anti-hypertensive medications: a narrative review. *Curr Hypertens Rep*. 2020;22(12):105. doi:10.1007/s11906-020-01115-4

Lifestyle Interventions

Case 4: *A 68-year-old woman with obesity and osteoarthritis presents with worsening BP control. She is discouraged because she has gained 12 pounds over the past year. Her husband passed away 6 months ago, and, as a result, she is cooking less at home as she adjusts to living alone. Fresh fruits and vegetables tend to go bad before she can finish them, so she is relying on canned soups, frozen dinners, and take-out meals. Previously, they had been going to the local senior center to take group exercise classes together at least 4 days a week, but she stopped going and has not found any suitable alternatives. In the past, she had been drinking alcohol only on weekends but is now having a glass of wine each night. Her BP in the office today (taken by AOBP) is 143/92 mm Hg. A year ago, her BP was measured at 127/78 mm Hg.*

Question 4: Which of the following nonpharmacologic strategies is likely to have the greatest impact on her BP?

(a) Counseling on reduced sodium options that fit her current life circumstances
(b) Referring to physical therapy for dynamic resistance training for 20 minutes twice a week
(c) Advising her to stop drinking alcohol
(d) Recommending losing 10 pounds over the next 2 months

For the answer to this question, see the following text.

Lifestyle interventions, also referred to as nonpharmacologic therapy, should be continuously assessed and addressed at every visit. Beyond improvement in BP control, nonpharmacologic therapies can also have halo effects that improve other common comorbidities seen in patients with RHTN. For example, sustained weight loss can improve diabetes, reduce pain from osteoarthritis, and lessen the severity of OSA. Lastly, making healthier lifestyle choices has independent benefits on overall cardiovascular risk.

There is ample evidence to support recommending increased physical activity, healthy diet changes, sodium reduction, alcohol moderation, and weight loss for all patients with hypertension, though not all of these have been studied specifically in patients with RHTN. Of these, sodium reduction may be the single most effective

strategy, perhaps in part related to the increased salt sensitivity that is seen in patients with RHTN, making the correct answer (a).

Notably, sodium reduction can also be synergistic with pharmacologic treatment with renin-angiotensin-aldosterone–blocking medications and can offset the hypokalemic effects of thiazide diuretics. Independent of sodium reduction, increasing dietary potassium intake can also lower BP, though care should be taken in patients who are at risk for hyperkalemia due to underlying CKD or treatment with medications that can increase serum potassium levels, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or potassium-sparing diuretics. The generally recommended method for increasing potassium intake is through the consumption of high-potassium foods rather than through supplements, though even substituting regular table salt with a salt substitute containing 75% sodium chloride and 25% potassium chloride was found to both reduce BP and decrease cardiovascular events. The Dietary Approaches to Stop Hypertension (DASH) diet is a generic diet pattern with a focus on vegetables and fruits, whole grains, lean protein sources, and low-fat dairy products that can be adapted to suit a variety of different ethnic or cultural backgrounds and food preferences.

Newer glucagon-like peptide 1 (GLP-1) receptor agonists (liraglutide, dulaglutide, and semaglutide) and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (tirzepatide) have drastically changed the treatment of both type 2 diabetes and obesity. Furthermore, these medications have also been demonstrated to have protective effects on the cardiovascular and kidney systems independent of hemoglobin A_{1c} reduction and weight loss. Though these medications have very modest direct BP-lowering impact, presumably through diuretic and natriuretic effects, longer-term use can contribute to lower BPs through their effects on body weight and insulin sensitivity.

It should be acknowledged that changes in habits and dietary modifications are notoriously difficult to achieve and maintain in the long term. Busy clinicians may find it challenging to find the time or lack the training to effectively counsel patients on how to make these changes. Using strategies such as motivational interviewing, helping patients set SMART (specific, measurable, achievable, relevant, and time-bound) goals, and using nonjudgmental language and shared decision making to set priorities can be helpful. Leveraging frequent follow-up with other care team members such as nutritionists, pharmacists, or physical therapists may also help with patient engagement. Where available, referring to a comprehensive structured program that incorporates more than one aspect of healthy lifestyle changes can be particularly effective.

Additional Readings

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Evaluating for Secondary Causes of Hypertension

Renal Artery Stenosis, Primary Aldosteronism, and Obstructive Sleep Apnea/Disordered Sleep

Case 5: *A 75-year-old man with longstanding hypertension, hyperlipidemia, coronary artery disease (CAD), OSA, osteoarthritis, and stage 4 CKD describes worsening BP control over the last few months. He had previously been able to keep his BP readings below 120/80 mm Hg on olmesartan 40 mg once daily, felodipine 10 mg once daily, and carvedilol 12.5 mg twice daily. However, his readings are now consistently above 150/90 mm Hg using his validated home BP cuff, which is confirmed with AOBP in the clinic. He is using his continuous positive airway pressure (CPAP) machine on a nightly basis. Laboratory testing reveals a baseline creatinine of 1.5 mg/dL, potassium of 3.2 mEq/L, and bicarbonate of 28 mEq/L. His plasma aldosterone concentration is measured at 12 ng/dL (reference range, <21, measured between 4 and 6 PM) and plasma renin activity is 0.15 ng/mL/hour (reference range, 0.25-5.82).*

Question 5: Which of the following is the next best step?

(a) Check 24-hour urine collection for aldosterone and sodium with high sodium intake.

(b) Stop olmesartan and carvedilol for 2-4 weeks and recheck serum aldosterone and renin.

(c) Refer for repeat polysomnography and CPAP mask refitting.
(d) Refer for adrenal venous sampling.

For the answer to this question, see the following text.

Primary aldosteronism is an increasingly common and underrecognized cause of RHTN, with an estimated prevalence as high as 20% in certain populations. This entity is defined by hypertension caused by near-autonomous secretion and inappropriate elevation of aldosterone, independent of plasma renin concentrations, leading to volume expansion primarily from sodium reabsorption and enhanced sympathetic nervous system activity. Important clues to primary aldosteronism include hypokalemia and metabolic alkalosis early on, with cardiovascular and kidney disease presenting as later findings. However, normokalemia is common and does not rule out the presence of primary aldosteronism. Compared to those with essential hypertension, individuals with primary aldosteronism have been observed to have increased risk of atrial fibrillation, myocardial infarction, heart failure, and stroke.

Given the high prevalence and significant risks, all individuals with RHTN should be screened with an aldosterone/renin ratio (ARR), consisting of plasma aldosterone concentration and plasma renin activity, ideally drawn from a patient in a seated position in the morning hours after potassium repletion if hypokalemic. Some would suggest that any degree of renin suppression (<1.0 ng/mL/hour) from a routine blood draw should raise suspicion for primary aldosteronism (assuming the aldosterone level is not also suppressed), regardless of the ratio. An ARR of >30, or >20 with plasma aldosterone of >15 ng/dL almost certainly represents primary aldosteronism.

Though many antihypertensive medications may influence plasma aldosterone concentration and plasma renin activity, selective withdrawal of offending medications before rechecking the ratio is typically unnecessary. Given the potential harms of severely elevated BP after the withdrawal of multiple antihypertensive agents with a concomitant delay in diagnosis, it is advisable and often still possible to interpret the ARR in the context of continuing these medications (with the exception of mineralocorticoid receptor antagonists [MRAs] and epithelial sodium channel blockers). Table 5 shows the effect of each class of antihypertensive agents on the ARR and how the results may be interpreted if the medication must be continued.

To decrease the rate of false-positive results, typically driven by renin suppression, it is often helpful to evaluate the plasma renin activity (PRA) and plasma aldosterone concentration (PAC) separately. Primary aldosteronism is unlikely if the PAC is less than 5-10 ng/mL. False negatives related to MRAs (and occasionally ACE inhibitors and ARBs) are more common, with a measured increase in renin activity. These medications, especially MRAs, can be selectively withdrawn with subsequent recheck of the ARR if suspicion remains high for primary aldosteronism.

If the ARR is positive and pretest probability is high, confirmatory testing is recommended in most cases. For those with ongoing hypokalemia, a highly suppressed PRA of <1 ng/nL/hour, and PAC of ≥20 ng/dL, confirmatory testing may not be necessary. The simplest confirmatory test is the saline suppression/infusion test. This protocol typically involves the infusion of 2 liters of 0.9% saline over 4 hours in the seated position from 8 AM to 12 PM, with aldosterone, renin, and potassium levels checked before and after infusion. If serum aldosterone production is sustained at >10 ng/dL, this is a positive confirmatory test. An oral salt-loading test is less resource intensive but requires a 3-day consumption of 5 grams of sodium per day. This is often achieved with a combination of food intake and sodium chloride tablets, with subsequent measurement of serum electrolytes and a 24-hour urine collection for sodium and creatinine (to confirm the efficacy of the salt load and an appropriately timed urine collection, respectively) as well as aldosterone. If a urine sodium of >200 mEq per 24 hours is achieved, then an elevated urine aldosterone excretion of >12 μg would confirm primary aldosteronism.

Some experts have suggested that saline suppression testing and salt loading may precipitate a hypertensive crisis, so they advocate for proceeding with collecting 24-hour urine for aldosterone while consuming a typical high-sodium American diet. The correct answer is (a): if a concurrently collected 24-hour urine sodium level is >200 mEq/L, the sample can be interpreted as one would with a protocolized sodium load (i.e., aldosterone > 12 μg/24 hours can be considered a positive confirmatory test). Others support the use of the intravenous saline suppression test because it is done in a closely monitored environment where any adverse effects of elevated BP could be attended to urgently if needed. Additional confirmatory testing options include the captopril challenge test and the fludrocortisone suppression test, both of which are cumbersome and less commonly done.

Once confirmed, an abdominal computed tomography (CT) scan with an adrenal protocol can distinguish between a unilateral aldosterone-producing adenoma and bilateral hyperplasia as well as rule out an adrenal carcinoma (rare). If surgical resection is not optimal due to high surgical risk or personal preference, medical management using MRAs is the standard of care, regardless of the subtype. If surgery is considered, adrenal venous sampling, performed at an experienced center, will help to determine if there is sufficient laterality for unilateral laparoscopic adrenalectomy.

In patients younger than 35 years with overt primary aldosteronism and a unilateral adrenal nodule > 1 cm,

Table 5. Effect of Antihypertensive Medication Classes on the Plasma Aldosterone Concentration to Plasma Renin Activity Ratio

Medication Class	Effect on PAC	Effect on PRA	Overall Effect on ARR	Interpretation of ARR if Medication Continued During Testing
β_1-Receptor antagonists	↓	↓↓	↑	Low PAC (<5 ng/dL) argues against PA even if renin activity is suppressed.
Central α_2-agonists	↓	↓↓	↑	
ACE inhibitors	↓	↑ ↔	↓	Low renin activity would be highly suggestive of PA. High renin activity would not rule out PA.
ARBs	↓	↑ ↔	↓	
Diuretics (loop and thiazide)	↔ ↑	↑↑	↓	Similar to ACE inhibitors/ARBs
MRA	↔ ↑	↑↑	↓	If renin not suppressed, MRA should be held for testing. Diagnosis of PA can be made if PAC is high and PRC is suppressed.
DHP calcium channel blockers	↔ ↓	↔ ↑	↓	Data are mixed, but may produce excess false-negative results.
α_1-Receptor antagonists	↔	↔	↔	Does not interfere with testing.
Direct arterial vasodilators	↔	↔	↔	
Non-DHP calcium channel blockers	↔	↔	↔	

Based on information in Jędrusik P, Symonides B, Lewandowski J, Gaciong Z. The effect of antihypertensive medications on testing for primary aldosteronism. *Front. Pharmacol.* 2021;12:684111. doi:10.3389/fphar.2021.684111. Abbreviations: ACE, angiotensin converting enzyme; ARR; aldosterone to renin ratio; ARB, angiotensin receptor blockers; DHP, dihydropyridine; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

adrenal venous sampling may not be necessary before proceeding to adrenalectomy. Patient with bilateral adrenal hyperplasia require lifelong medical therapy with MRAs, titrated as tolerated to achieve a serum potassium level of 4.5 mEq/L and a target BP of <130/<80. New data have suggested that targeting renin > 1 ng/nL/hour may also decrease cardiovascular events and improve renal outcomes (i.e., a slower decline in estimated glomerular filtration rate).

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Case 6: *A 45-year-old woman with hypothyroidism presents to the clinic with hypertension that has been difficult to control. She is currently taking chlorthalidone 25 mg once daily, verapamil extended release 240 mg once daily, carvedilol 25 mg twice daily, and valsartan, which was recently increased from 160 mg once daily to twice daily. Her baseline creatinine level is around 1.1 mg/dL, but it has recently been elevated to 1.8 mg/dL over the last 2-3 months, as confirmed on recheck a few weeks later. Her electrolyte panel is notable for potassium of 4.9 mEq/L and bicarbonate of 22 mEq/L.*

Question 6: Which of the following studies should be done first?

(a) Abdominal CT scan with an adrenal protocol
(b) Polysomnography
(c) Renal angiography
(d) Renal duplex ultrasound of renal arteries

For the answer to this question, see the following text.

Renal artery stenosis (RAS) is quite common among those with RHTN, especially among older individuals with known vascular disease, atherosclerosis, smoking history, diabetes mellitus, and CKD. The severity of RAS is often determined by the diagnosis of accelerated hypertension and progressive kidney dysfunction, and moderate degrees of renovascular hypertension are often managed with renin-angiotensin-aldosterone system blockade without issue. Although most individuals will tolerate ACE inhibitor or ARB therapy, a small fraction may develop acute kidney injury, especially if concurrently on diuretics.

Duplex ultrasound imaging is the most common initial imaging test performed in those with a high pretest probability of a RAS diagnosis, so the correct answer is (d). Peak systolic velocity (PSV) is the most important direct evaluation of a stenotic area, and elevated PSV is among the most sensitive and specific ultrasound criterion for a RAS diagnosis. However, PSV may be slightly elevated in all arteries in the setting of hypertension, so some proponents will compare the PSVs of the renal artery and aorta (renal/aortic ratio) for a more reliable measure, where an elevated renal/aortic ratio is highly suggestive of RAS. Because direct measurements of the stenotic region can be technically challenging, others have focused their efforts on identifying abnormal waveforms distal to the stenosis.

The most common abnormality seen in RAS is the "tardus-parvus" waveform, where the distal flow of the renal artery shows a slow rise (tardus) to a lower systolic peak (parvus). In cases with ambiguous or contradictory results, confirmation by CT or magnetic resonance angiography (with consideration of the safety of iodinated or gadolinium contrast exposure if kidney function is decreased) is necessary. Given the technical difficulty of renal artery duplex testing, especially in those with a body habitus complicating ultrasound image acquisition, a negative result should not dissuade further testing in those with high pretest probability of having RAS.

Additionally, although plasma renin activity may be elevated in RAS, this measurement is not helpful in establishing a diagnosis because it can be suppressed by a high-sodium diet and influenced by multiple medications (as per Table 5). On initial ultrasound, kidney asymmetry, or the relatively new appearance of bilateral kidney atrophy, may also provide important contextual clues into the chronicity and laterality of RAS.

The CORAL study, along with older trials including ASTRAL and STAR, suggested that medical therapy plus vascular intervention did not result in improved outcomes compared with medical therapy alone, though the study was limited by likely under-enrollment of the most hemodynamically significant renal artery stenoses.

Before performing imaging, it is also important to consider which individuals are the most likely to benefit from invasive intervention of a discovered stenotic lesion, including those with a solitary kidney or severe bilateral disease with rapidly rising creatinine, significant acute kidney injury in the presence of an ACE inhibitor/ARB and a diuretic, documented fibromuscular dysplasia (especially common among younger women), or known RAS with flash pulmonary edema. In those individuals who are not candidates for invasive intervention, imaging studies may not be indicated. Aspirin and statin initiation along with smoking cessation should be considered for any individual with suspected RAS who develops refractory hypertension despite optimal medical therapy.

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Case 7: *A 36-year-old woman with obesity (BMI > 40 kg/m^2), type 2 diabetes mellitus, and hyperlipidemia presents with a new diagnosis of hypertension. Despite successfully losing 30 pounds over the summer, she has been unable to keep the weight off in the subsequent winter months. She joined a gym, but chronic back and knee pain have prevented her from a regular exercise routine. With these efforts, discontinuation of all NSAIDs for her pain control, and initiation of lisinopril at 20 mg daily, her BP is mildly improved to 145/83 mm Hg on AOBP in the clinic. She is provided with a 24-hour ABPM before referral for polysomnography testing.*

Question 7: Which of the following findings on 24-hour ABPM would be most suggestive of a diagnosis of OSA?

(a) Elevated BP readings between 3 PM and 5 PM.
(b) Elevated BP readings between 12 AM and 5 AM.
(c) Low BP readings between 6 PM and 9 PM.
(d) Low BP readings upon awakening at 7 AM.

For the answer to this question, see the following text.

Disordered sleep may lead to RHTN through overactivation of the sympathetic nervous system and the renin-angiotensin aldosterone system, both implicated in sleep deprivation, restless leg syndrome, and OSA. This overactivation leads to paroxysms of elevated BP in some and an overall increase in sympathetic tone in others. Screening for symptoms of OSA, including snoring, excessive daytime sleepiness or sleep partner reports of frequent nighttime awakenings or apneic episodes, is the easiest way to uncover this disorder. OSA remains highly prevalent in individuals with RHTN, characterized by intermittent hypoxia episodes that track with nighttime

increases in BP ("nondipping") as in Case 7 making the correct answer (b).

Increased fluid retention along with supine positioning may increase upper airway edema in those at highest risk, which may improve with diuretic therapy. It is important to keep in mind, however, that nocturia from diuretics may further impair sleep quality without any net positive effect on hypertension management. Although CPAP treatment for at least 4 hours per night can result in a 2-5 mm Hg drop in systolic BP (though even more in those with superior adherence or RHTN), adjunctive pharmacologic agents targeting these systems, including long-acting ARBs, α-β blockers, and central α_2-agonists given at bedtime, remain essential.

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Chronic Kidney Disease

Hypertension is highly prevalent among those with CKD. Increased activity of both the renin-angiotensin-aldosterone system and sympathetic nervous system due to decreased overall glomerular filtration rate leads to sodium avidity and subsequent volume expansion. Along with the direct deleterious effects of sodium on the vasculature itself, leading to accelerated arteriosclerosis, the ongoing sodium and water reabsorption complicate the treatment of hypertension in the CKD population.

It is important to recognize and treat hypertension early in these patients because studies have shown increasing difficulty in achieving BP targets in later stages of CKD. The CLICK trial showed that thiazide diuretics can be used safely and effectively alongside loop diuretics in this population to help counteract the volume overload that leads to hypertension. Dietary sodium restriction remains the cornerstone of treatment, increasing the efficacy of antihypertensive medications and potentially slowing CKD progression.

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Endocrine Disorders

Although there are a variety of additional endocrine disorders that can lead to hypertension, they are much less common. Table 6 provides brief descriptions of these conditions.

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Optimizing Pharmacologic Therapies

Case 8: *A 72-year-old man with heart failure with reduced ejection fraction, stage 4 CKD, and a diagnosis of hypertension since his early 30s, presents to the clinic 3 months after a non-ST elevation myocardial infarction. His BP has remained uncontrolled, with an AOBP reading of 164/63 mm Hg, despite lisinopril 40 mg once daily, amlodipine 5 mg twice daily, and metoprolol 100 mg twice daily. Recent laboratory testing shows acute kidney injury, with creatinine elevated to 3.4 mg/dL (baseline 2.5 mg/dL), as well as potassium (K^+) of 5.4 mEq/L.*

Question 8: Which of the following medication adjustments is indicated at this time?

(a) Addition of daily eplerenone at 25 mg
(b) Substitution of twice daily metoprolol at 100 mg with daily bisoprolol at 10 mg
(c) Decrease of daily lisinopril to 20 mg and addition of daily chlorthalidone at 12.5 mg
(d) Discontinuation of lisinopril with replacement of daily spironolactone at 25 mg

For the answer to this question, see the following text.

The diagnosis of RHTN requires a BP above 130/80 despite confirmedadherence to 3 antihypertensive medications of differing classes. These medication classes often include renin-angiotensin-aldosterone system blockers (including ACE inhibitors or ARBs), dihydropyridine CCBs, and a diuretic (typically a thiazide), all at maximum or maximally tolerated doses. Thiazide-like diuretics, such as chlorthalidone and indapamide, have longer half-lives than hydrochlorothiazide and tend to be

Table 6. Less Common Endocrinologic Etiologies of Secondary Hypertension

Condition	Clinical Clues to Diagnosis	Screening Tests	Additional Evaluation or Confirmatory Testing
Pheochromocytoma / paraganglioma	• Paroxysmal hypertension + headache, palpitations, pallor and "cold sweat" • Family history of diagnosis	Levels typically >4 times the upper limit of normal in: • Plasma free metanephrines (preferred initial test, with high sensitivity and specificity) • 24-Hour urinary fractionated metanephrines (highest sensitivity, but prone to collection error) Note that false-positive results may occur in the setting of tricyclic antidepressants, other medications interfering with adrenergic receptors, and physical stress/illness (ie, during hospitalization).	CT or MRI of abdomen and pelvis (95% of tumors). Imaging characteristics include: • >3 cm • increased vascularity • >20 HU on noncontrast CT • high signal intensity of T2-weighted MRI Note that 40% of these tumors are due to germline variant, for which genetic testing for VHL, MEN2, NF1, and SDH variants should be performed in all patients with a confirmed diagnosis.
Cushing syndrome	• Changes in mood • Altered menstruation patterns • Proximal muscle weakness or atrophy • Easy bruising • Weight gain along with abdominal striae • Hirsutism • Dorsal and/or supraclavicular fat • Difficulties with glucose control	First-line testing includes (initial testing varies by center, often repeated for those with higher suspicion): • Bedtime salivary cortisol • 24-Hour urinary free cortisol excretion • Overnight dexamethasone suppression testing	• Rule out physiologic hypercortisolism (physical or psychological stress, alcohol withdrawal, morbid obesity, pregnancy). • Endocrinology referral
Hypothyroidism	• Constipation • Cold intolerance • Dry/cold skin • Weight gain	TSH (high) and low/normal free T_4	Not applicable
Hyperthyroidism	• Diarrhea • Heat intolerance • Moist/warm skin • Weight loss • Tremulousness • Proximal muscle weakness	TSH (low) and high/normal free T_4 and T_3	Radioactive iodine uptake and scan
Apparent mineralocorticoid excess	• Hypokalemia and metabolic alkalosis • Arrhythmias • Licorice ingestion • Triazole antifungal medications (ie, posaconazole)	Low aldosterone and low renin levels	• Urinary free cortisol/cortisone ratio (defective 11-β HSD2 enzyme leads to very low cortisone and high ratio) • Deoxycortisone levels • Genetic testing for Liddle's syndrome (milder phenotypes can present later in life)

Based on information in Carey RB, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension.* 2018:72(5):e53-e90. doi:10.1161/HYP.0000000000000084. Abbreviations: CT, computed tomography; HSD2, hydroxysteroid dehydrogenase 2; HU, Hounsfield units; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; NF1, neurofibromatosis 1; SDH, succinate dehydrogenase complex; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone; VHL, Von Hippel-Lindau syndrome.

more effective antihypertensive agents within this class. Further, the hypokalemic effects of thiazides can be beneficial which makes (c) the correct answer. Different formulations of these medications are available as double and triple fixed-dose combination pills, designed to improve adherence and achieve target BPs more quickly. Despite being the backbone of antihypertensive therapy in all patients, these 3 medication classes all have side effects, so maximizing their dosing may be limited and additional antihypertensive therapies may need to be employed in a stepwise fashion.

Given the significant evidence supporting their efficacy as well as the high prevalence of undetected hyperaldosteronism, MRAs should be considered after maximizing the first-line agents. Hyperkalemia, especially in the setting of ongoing ACE inhibitors or ARB therapy and CKD, is the most common adverse effect of MRAs; this can be managed with dose modification of existing medications, including adding or increasing diuretics (as in the case above) or the addition of the newer potassium binders. In fact, loop diuretics also may be considered a second-line pharmacologic therapy, though attention should be paid to the duration of action of the available agents.

Longer-acting options with high oral bioavailability such as torsemide are preferred over shorter-acting agents such as

furosemide that have less predictable bioavailability and require multiple daily doses. Although non-dihydropyridine CCBs may have mild antiproteinuric effects in combination with renin-angiotensin-aldosterone system inhibitors, their BP-lowering effects have not been compared with newer agents of particular utility in the setting of proteinuria (i.e., sodium/glucose cotransporter 2 [SGLT2] inhibitors or GLP-1 receptor agonists). Regardless of proteinuria status, a non-dihydropyridine CCB can, in some circumstances, be added safely to a regimen that already includes a dihydropyridine CCB.

Anyone who requires 5 or more medications for BP management, regardless of whether the BP has reached the target, should be considered to have *refractory* hypertension, a subtype of RHTN. Because the overactivation of the renin-angiotensin-aldosterone system and its resulting volume overload has presumably been fully addressed by this regimen, additional antihypertensive medications should then be focused on suppressing excess sympathetic nervous system activity.

Many clinicians may find that their patients are already taking sympatholytic agents such as β-blockade (typically with α activity for vasodilatory effect) due to comorbidities such as heart failure, atrial fibrillation, or recent myocardial infarction, given their overall mortality benefit in these patient populations. Due to additional vasodilatory effects of α_1 blockade on the vasculature, dual α-β receptor blockers such as carvedilol and labetalol are preferred over β-selective medications, including metoprolol or bisoprolol, if the primary indication is for BP management. Additional sympatholytic agents with antihypertensive action include central α_2-agonists (clonidine, guanfacine), α_1 antagonists (doxazosin), and direct arterial vasodilators (hydralazine, minoxidil), all of which can be quite effective when utilized in this context but can also lead to significant adverse effects, attenuating their long-term use.

Although they are generally not considered antihypertensive agents per se, SGLT2 inhibitors can provide modest BP-lowering effects in addition to other benefits in appropriate patients with certain comorbidities, particularly concurrent type 2 diabetes mellitus, CKD, and/or heart failure. New pharmacologic agents that aim to treat hypertension at novel target sites, such as aldosterone synthase inhibitors and endothelin receptor antagonists, have either been recently approved or are currently in phase 3 clinical trials. Our pharmacologic approach to RHTN is shown in Figure 2.

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Renal Denervation

Case 9: *A 67-year-old woman with a past medical history of type 2 diabetes and gout presents for follow-up evaluation of her hypertension. She is taking valsartan 320 mg once daily. In the past, she developed severe hyponatremia on thiazide diuretics and spironolactone. She has been unable to take β-blockers or α-agonists due to bradycardia. She experienced a lupus-like syndrome while taking hydralazine and had gingival hyperplasia on amlodipine. AOBP in the office is 151/93 mm Hg. Her 24-hour ABPM shows a daytime average BP 149/91 mm Hg. She is worried about high BP because her younger sister recently had a stroke. She asks whether she is a candidate for renal denervation (RDN).*

Question 9: Which of the following is true regarding RDN?

(a) Beneficial effects of RDN have been limited to patients with RHTN.
(b) RDN may be recommended in patients with multiple medication intolerances.
(c) Second-generation sham-controlled trials showed an increased risk of RAS.
(d) RDN can be expected to lower systolic BP by 10-12 mm Hg.

For the answer to this question, see the following text.

Sympathetic nerve hyperactivity, particularly at the level of the renal nerves, is a known contributor to RHTN. RDN is a novel nonpharmacologic treatment that can lower BP by targeted catheter-based treatments to ablate the renal sympathetic nerves. Initial enthusiasm for this technology was subsequently lessened by the results of SYMPLICITY HTN-3, a sham-controlled trial that failed to show significant benefit. However, several of the subsequent second-generation, randomized, sham-controlled trials did show BP-lowering effects, which has revitalized interest in this technology. The safety concerns thus far have been minimal, and newer studies have shown potential benefit in a broad spectrum of patients, both on and off pharmacologic treatment.

Most of these trials have shown a modest average systolic BP reduction when compared with the sham-controlled group, ranging from 4-7 mm Hg. Of note, the currently published sham-controlled trials have had relatively short follow-up intervals and have excluded patients with estimated glomerular filtration rates of <30 mL/min/1.73 m^2.

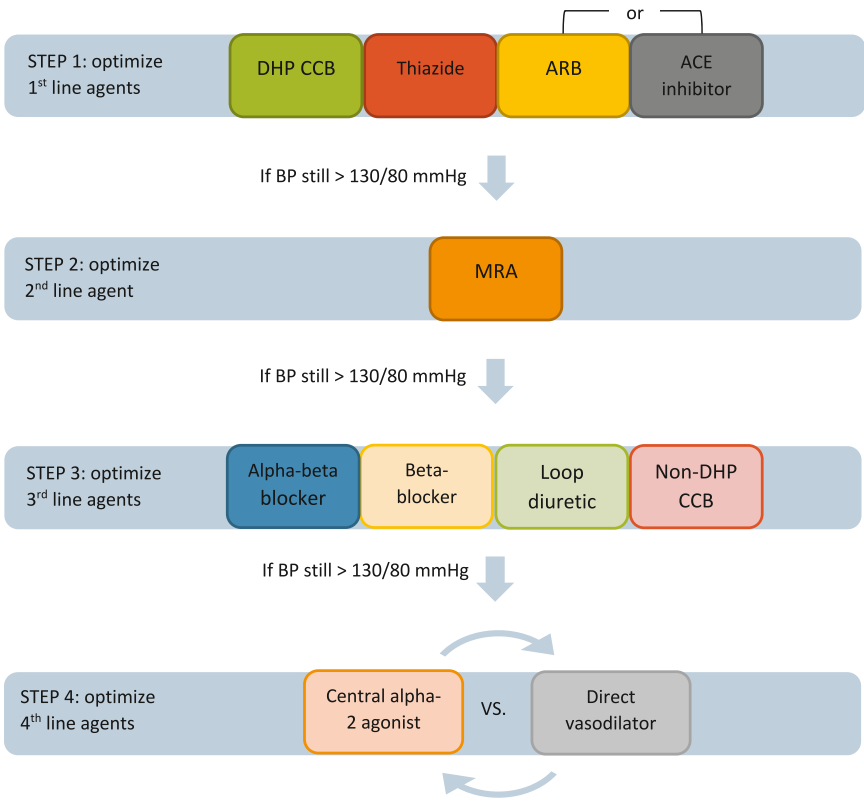

Figure 2. Pharmacologic management of resistant hypertension. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DHP CCB, dihydropyridine calcium channel blocker; MRA, mineralocorticoid receptor antagonist.

RDN was approved by the United States Food and Drug Administration in late 2023 for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of antihypertensive medications or in patients who have documented intolerance to antihypertensive medications as in Case 9, so the correct answer is (b).

Further work in the field is needed to determine optimal patient selection as well as the long-term benefits and safety risks.

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Article Information

Authors' Full Names and Academic Degrees: Jennifer L. Cluett, MD, and Jeffrey H. William, MD.

Authors' Affiliations: Division of General Internal Medicine (JLC), Division of Nephrology (JHW), and Complex Hypertension Clinic (JLC, JHW), Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Address for Correspondence: Jeffrey H. William, MD, Division of Nephrology, Department of Medicine, Beth Israel Deaconess Medical Center, 171 Pilgrim Rd, Boston, MA 02215. Email: jhwillia@bidmc.harvard.edu

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