Resistant hypertension is common in the chronic kidney disease population and conveys increased risk for adverse cardiovascular outcomes and the development of kidney failure. Recently, the American College of Cardiology and American Heart Association published a revised scientific statement on the definition and management of resistant hypertension, which codified the long-debated differences between pseudoresistant hypertension and true resistant hypertension. We review this distinction and its importance to nephrologists, who frequently encounter patients for whom antihypertensive therapy fails due to difficulty adhering to complex multidrug regimens. Second, we discuss the evaluation of patients with resistant hypertension, including appropriate screening and diagnostic testing for causes of secondary hypertension. Third, we examine the management of established resistant hypertension, including medication optimization, recent clinical trials supporting lifestyle modifications, and the evidence behind the routine use of mineralocorticoid receptor antagonists. Special attention is given to the vital role of diuretics in the treatment of patients with chronic kidney disease. We propose an algorithm for the diagnosis and management of these cases. Finally, we briefly discuss the current state of antihypertensive device therapies, including kidney denervation and baroreceptor-directed therapies.

Introduction
Hypertension is a leading risk factor for the development of cardiovascular disease and is increasing in prevalence. Despite increases in awareness and treatment, hypertension continues to be responsible for more combined years of life lost and years lived with disability than any other cause of morbidity and mortality. Reduction in blood pressure (BP) reduces the risk for end-organ damage, and patients who do not reach BP goals despite multidrug therapy are designated as having resistant hypertension (RH). This diagnosis confers significant downstream effects on patient management and prognosis. Establishing an accurate diagnosis is not straightforward and a standardized approach is necessary.

RH is common in individuals with chronic kidney disease (CKD) and becomes more prevalent with declining kidney function. Masked hypertension (MH), defined as elevated ambulatory BP with normal office BP, is present in ~30% of patients with CKD and is more likely to be associated with RH and end-organ damage. Among individuals with CKD, RH is associated with greater risk for kidney disease progression; therefore, an understanding of recent definitions and therapeutic options is crucial for nephrologists engaging in the care of patients with CKD. This review discusses a stepwise approach to the diagnosis and evaluation of RH with special focus on the patient with CKD.

Definition of RH
In 2018, the American Heart Association (AHA) issued a revised scientific statement on the detection, evaluation, and management of RH (Box 1), which reflected the progressive understanding of disease pathogenesis since their first consensus statement in 2008. The core definition of RH was unchanged: BP that remains elevated despite treatment with 3 maximally dosed (or maximally tolerated) medications of different classes, ideally including a diuretic. RH also includes reaching target BP values with 4 or more antihypertensive medications (ie, controlled RH).

This definition alone identifies patients with apparent RH. The authors therefore modified diagnostic criteria to include: (1) ensuring accurate BP measurements and BP targets in accord with current clinical practice guidelines, (2) using out-of-office BP monitoring to rule out the “white-coat effect,” and (3) verifying adherence to prescribed antihypertensive medication therapy. These criteria distinguish pseudo-RH, which is managed with better BP monitoring and medication adherence, from true RH, which warrants further workup and therapy modification.

Epidemiology of RH
The prevalence of true RH is unknown but estimates range from 2% to 40% in treated hypertensive populations. Studies quantifying RH often lack a uniform definition of RH and these publications typically measure apparent RH due to a failure to assess medication dosing, medication adherence, or out-of-office BP measurements. This has led to an overestimation of the true prevalence of RH.

An analysis of more than 3,300 patients in the Chronic Renal Insufficiency Cohort (CRIC) Study, a multicenter prospective observational study of adults with estimated glomerular filtration rates (eGFR) of 20 to 70 mL/min/1.73 m², found the prevalence of apparent RH among hypertensive patients to be 40.4%. However, the white-coat effect has been observed in as many as one-third of individuals with apparent treatment resistance, and numerous studies have shown medication nonadherence in 50% to 80% of patients with RH diagnosed.
Box 1. Definition of RH

**Components of Definition**
- BP that remains elevated above the patient’s individualized target despite the concurrent use of 3 antihypertensive agents of different classes, ideally including a diuretic, administered at maximum or maximally tolerated doses and at the appropriate dosing frequency.
- BP that is controlled to the patient’s individualized target with ≥4 antihypertensive medications, ideally including a diuretic, administered at maximum or maximally tolerated doses and at the appropriate dosing frequency (ie, controlled RH).

**Differentiating Pseudoresistant Hypertension From True RH**
- The BP threshold for diagnosis and treatment goals should be in accord with current clinical practice guidelines.
- Ensure proper technique in BP measurement.
- Exclude "white-coat hypertension" by performing out-of-office BP measurements.
- Exclude antihypertensive medication nonadherence.

Abbreviations: BP, blood pressure; RH, resistant hypertension. Definition based on Carey et al.5

In cases in which adherence was measured, data were often based on patient self-reporting, which can be misleading. One retrospective study that assessed adherence using prescription filling information in more than 200,000 hypertensive patients found that only 1.9% of adherent patients developed RH during 1.5 years of follow-up.15 American College of Cardiology/AHA guidelines from 2017 reduced the BP goal of treatment to <130/80 mm Hg for most individuals, which will undoubtedly increase the prevalence of RH.14

Despite difficulty quantifying RH, current evidence demonstrates an increased risk for adverse cardiovascular and kidney outcomes in patients with apparent RH compared with patients with treatment-responsive hypertension.6,15,22 Differences in cardiovascular events may be largely driven by increased risk for the development of CKD.5,15 One retrospective study of more than 400,000 patients found that those with apparent RH had greater risk for kidney failure, ischemic heart events, heart failure, stroke, and death compared with patients without RH.13 Specifically, risk for the development of kidney failure was 25% greater in patients with uncontrolled RH compared with those who achieved BP targets.

Diagnosing True RH

**Accuracy of BP Measurements**

Errors in BP measurement are common both in and out of the office, even when performed by experienced clinic staff.24 Recommendations for obtaining accurate office BP values are shown in Box 2.14,25-27 The white-coat effect is common with apparent RH and more pronounced than in

**Box 2. Correct BP Measurement Technique**

**Step 1: Preparation**
- a. The patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement.
- b. Ensure that the patient has emptied his or her bladder.
- c. Remove all clothing covering the location of cuff placement.
- d. The patient should relax, sitting down with feet flat on the floor and back supported, for at least 5 min at an adequate room temperature (~72 °F). Neither the patient nor the measurer should talk during the rest period or during BP measurement.

**Step 2: Use proper technique**
- a. Use a BP device that has been validated and periodically calibrated.
- b. If a manual (mercury or aneroid) sphygmomanometer is used, a stethoscope must be used for auscultation of Korotkoff sounds.
- c. Support the patient’s arm (eg, resting on a flat surface).
- d. Position the middle of the cuff on the patient’s upper arm at the level of the right atrium (the midpoint of the sternum).
- e. Ensure correct cuff size, such that the bladder encircles 75%-100% of the arm.
- f. The center of the bladder (commonly marked by the manufacturer) should be placed over the arterial pulsation of the patient’s bare upper arm.

**Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension**
- a. At the patient’s first office visit, record the BP in both arms. Use the arm that gives the higher reading for subsequent measurements.
- b. For auscultatory measurements, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Then inflate the cuff 20-30 mm Hg above this level at the start of the subsequent measurement.
- c. For auscultatory measurements, deflate the cuff pressure 2 mm Hg per second and listen for Korotkoff sounds.
- d. Separate repeated measurements by 1-2 min.

**Step 4: Properly document the BP readings**
- a. Record SBP and DBP. If using an auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number.
- b. If taking repeated measurements, document the average SBP and DBP obtained across measurements.
- c. Record the time of the most recent BP medication taken before measurements.

**Step 5: Average multiple BP readings**

Use the average of ≥2 readings obtained on ≥2 occasions to estimate the patient’s level of BP.

**Step 6: Provide BP readings to patient**

Tell the patient the SBP/DBP readings, and also give the patient a written record of the readings.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Based on information from Whelton et al,14 Mancia et al,27 Pickering et al,26 and Weir.27
patients without hypertension.\textsuperscript{17,28-30} Verification of in-office BP measurements with 24-hour ambulatory BP monitoring (ABPM) is necessary in the evaluation of suspected RH. When ABPM is unavailable, home BP monitoring (HBPM) is an acceptable alternative.\textsuperscript{31}

Patients with CKD have increased risk for MH, which may be due to the higher prevalence of nocturnal nondipping in this population. Nondipping is a strong predictor of cardiovascular disease, kidney failure, and death. ABPM is useful to detect nondipping and is preferred over HBPM for identifying MH in patients with advanced CKD.\textsuperscript{32} If white-coat effect or MH is established, HBPM or ABPM should be used to guide further management decisions.\textsuperscript{12} Recommendations for HBPM are shown in Box 3.\textsuperscript{33}

**Medication Nonadherence**

Medication nonadherence is likely present in most individuals undergoing evaluation for RH. Prior studies have shown that strict adherence to prescription medications is present in only 1 of 6 patients being treated for chronic hypertension.\textsuperscript{17,28-30} Verification of drug metabolites in the blood or urine of patients who claim adherence.\textsuperscript{17-21} In one study of patients referred for RH, 65% were able to achieve BP targets when treated with directly observed therapy.\textsuperscript{17} Compared with patients without kidney disease, patients with CKD are more likely to be nonadherent to therapy, possibly due to medication complexity.\textsuperscript{18,38} Improving adherence by using simplified medication regimens with combination therapy, use of electronic medical records, telemonitoring, and patient self-management are important components in the evaluation and management of apparent RH.

There is no gold standard for measuring adherence, and clinician ability to detect nonadherence is poor.\textsuperscript{5,39} Direct urine or blood measurements are expensive and give rise to ethical issues, and directly observed therapy is impractical. Indirect methods assessing adherence such as pill counting, Medication Event Monitoring Systems, and patient self-reporting can be distorted, although prescription refill rates in a closed pharmacy system (eg, the Veterans Affairs Healthcare System and countries with universal health care coverage) have been shown to be accurate when measured at several time points.\textsuperscript{50,41} Techniques to help patients engage in candid discussion include improving physician-patient relationships, using non-accusatory language during interviews regarding adherence, and giving patients “permission” to answer questions honestly.\textsuperscript{5,34}

Clinicians must be aware of potential barriers to adherence and routinely minimize these barriers for patients. Remediable barriers include socioeconomic factors, treatment complexity, adverse medication effects, and patient motivation. Motivation is commonly affected by depression, lack of belief in the benefit of treatment, and lack of insight into illness.\textsuperscript{34} Medications should preferentially include low-cost and generic antihypertensives.\textsuperscript{42} Adherence is inversely proportional to the frequency of dosing, so once-daily medications and combination antihypertensive formulations should be used when available.\textsuperscript{43-46} Adverse medication effects should be addressed because patients may be reluctant to continue noxious therapies for an otherwise asymptomatic disease. Patients require education and should be allowed to participate in management decisions, which may improve adherence.\textsuperscript{45,47,48} Depression, if present, should be treated.

**Evaluation of RH**

When true RH is diagnosed, a thorough history and physical is performed to identify factors contributing to disease resistance and rule out secondary causes of hypertension. Lifestyle factors contributing to the development of RH, such as excessive sodium intake, excessive alcohol intake, sedentary lifestyle, and obesity, should be noted in the history as potential targets for therapeutic intervention.

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**Box 3. Guidance for Conducting HBPM**

**Patient Training**
- Provide information about the diagnosis and treatment of hypertension.
- Demonstrate proper BP measurement technique and provide information so accurate readings may be obtained at home (see Box 2).
- Ask the patient to bring the HBPM device and readings to health care visits.
- Provide education that individual BP readings may vary greatly over the monitoring period.

**Preferred Devices**
- Use a validated upper-arm oscillometric device.
- Use a cuff properly sized to the patient’s arm.
- Use a device that automatically stores BP readings and can ideally either print results or send them electronically to the health care provider.

**Number and Duration of Readings**
- Take 4 total readings daily: 2 readings at least 1 min apart in the morning before taking antihypertensive medications and 2 readings at least 1 min apart in the evening before going to bed.
- The preferred monitoring period is ≥7 d (ie, ≥28 total readings) ideally in the period immediately before an appointment with a health care provider or after medication adjustments have occurred. A minimum of 3 d (ie, 12 readings) may be sufficient.
- Monitoring over consecutive days is ideal.

**Analyzing Readings**
- The average SBP and DBP for all readings should obtained and recorded.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; SBP, systolic blood pressure.

Based on information in Muntner et al.\textsuperscript{22}
A comprehensive cardiovascular examination is necessary. BP should be measured in both arms while seated and in the thigh while supine to screen for aortic coarctation; a thigh systolic BP (SBP) > 10 mm Hg lower than arm SBP should prompt referral for imaging. In a patient with absent or diminished pulses, Takayasu arteritis should be excluded. The carotid arteries and abdomen should be auscultated for bruits, which increase the likelihood of renal artery stenosis.

Laboratory evaluation of RH includes a basic metabolic profile, urinalysis to screen for underlying nephritic or nephrotic syndrome (urinary protein > 2+ and/or urinary blood > 2+), plasma aldosterone concentration, and plasma renin activity to screen for primary aldosteronism (PA).

Interfering Medications
There are numerous classes of pharmacologic agents that potentially exacerbate hypertension (Box 4).49 A thorough medication reconciliation is important because several offending medications are often unmentioned during routine clinic visits, such as nonsteroidal anti-inflammatory drugs, over-the-counter cold medications, oral contraceptive pills, and illicit substances. Estrogen-containing oral contraceptive pills (including low-dose estrogen) have been associated with reversible malignant hypertension and should be avoided in favor of progesterone-based oral contraceptive pills in high-risk patients with RH.50

Obstructive Sleep Apnea
Obstructive sleep apnea (OSA) is strongly associated with RH and should be screened for as part of RH evaluation.51 Bedside screening tools can help determine when to refer for polysomnography.52 A causative relationship between OSA and RH has not been established, but randomized trials and meta-analyses have shown that continuous positive airway pressure produces a modest though clinically significant reduction in BP in patients with OSA, and that there is a dose-dependent relationship with increasing continuous positive airway pressure adherence.53

Secondary Hypertension: Diagnosis and Management
Chronic Kidney Disease
CKD increases BP through several mechanisms, including impaired sodium excretion and premature vascular ageing, which subsequently reduce baroreceptor sensitivity, increase sympathetic nervous tone, and activate the renin-angiotensin-aldosterone system.54 Underlying intrinsic kidney diseases such as glomerulonephritides can also cause hypertension. It is difficult to distinguish whether RH is primarily due to underlying CKD or secondary causes, but BP in progressive stage 4-5 CKD can be very elevated and difficult to control. However, secondary hypertension is common in CKD and should be suspected if signs or symptoms of a secondary cause are identified, such as unprovoked hypokalemia in a patient with CKD receiving renin-angiotensin-aldosterone system blockade, or accelerated CKD progression in a long-term smoker with vascular disease.55

Sodium homeostasis is paramount in the evaluation and management of comorbid CKD and RH. The KDOQI (Kidney Disease Outcomes Quality Initiative) hypertension guideline recommends limiting sodium intake to 2,400 mg/d for patients with CKD with hypertension.55 Randomized trials have shown significant BP reduction.

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**Box 4. Drug Classes With the Potential to Elevate Blood Pressure**

**Prescription Medications**

- Anticonvulsants
  - Carbamazepine
- Antidepressants
  - Monoamine oxidase inhibitors
  - Selective norepinephrine reuptake inhibitors
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
- Antiemetics
  - Metoclopramide
  - Prochlorperazine
- Antineoplastic agents
  - Paclitaxel
  - Tyrosine kinase inhibitors
  - Vascular endothelial growth factor (VEGF) inhibitors
- Antipsychotics
  - Clozapine
  - Thioridazine hydrochloride
- Calcineurin inhibitors
  - Cyclosporin
  - Tacrolimus
- Contraceptives
  - Low- and high-dose estrogen-containing formulations
- Erythropoietin
- Glucocorticoids
- Mineralocorticoids

**Nonprescription Medications**

- Amphetamines
- Caffeine
- Cocaine
- Ethanol
- Decongestants
  - Phenylephrine hydrochloride
  - Pseudoephedrine hydrochloride
- Herbal Supplements
  - Blue cohosh
  - Citrus aurantium-containing products, typically marketed for weight loss
  - Ephedra alkaloid-containing products (eg, Ephedra sinica, Ma huang), typically marketed for weight loss and athletic enhancement
- Nonsteroidal anti-inflammatory drugs
Aldosterone concentration is 1.73 m² and either resistant edema or uncontrolled hy-
pressions, loop diuretics should be used and can be added to an existing regimen that may include a thiazide diuretic. Chlorthalidone and indapamide have longer half-lives, are administered twice daily, whereas torsemide may be dosed once daily. At lower eGFRs, patients may require increased doses of loop diuretics. Similar to the management of patients receiving maintenance dialysis, diuretics should be titrated upward until patients either achieve BP goals or reach a “dry weight,” below which further diuresis leads to signs of volume depletion. In advanced CKD and RH, there is often improvement in BP control when dialysis is initiated because hypertension is largely mediated by sodium homeostasis and volume overload.

Primary Aldosteronism
The prevalence of PA in patients with RH is 11% to 23% and screening with plasma aldosterone concentration and plasma renin activity is mandatory when evaluating RH. Although classically associated with hypokalemia and metabolic alkalosis, these findings are present in only a minority of patients with PA. Screening is positive when plasma renin activity is <1 ng/mL per hour and plasma aldosterone concentration is ≥15 ng/dL. Further testing to confirm PA is usually required. Renin/aldosterone profiling can also be useful to distinguish salt sensitivity and can be used to tailor medical therapy in patients with RH even when they do not meet criteria for PA.

Compared with patients with essential hypertension, patients with PA have more rapid eGFR decline, increased left ventricular mass, and increased relative risk for stroke, myocardial infarction, and atrial fibrillation. These risks are attenuated but persist despite treatment with aldosterone antagonists. Adrenalectomy for unilateral aldosterone-producing adrenomas or unilateral adrenal hyperplasia likely mitigates these risks. Potential surgical candidates with confirmed PA should be offered adrenal vein sampling to assess for lateralizing disease and, if confirmed, require referral for surgical resection. Nonsurgical candidates are treated with aldosterone antagonists if tolerated or if not, potassium-sparing diuretics.

Renal Artery Stenosis
Renal artery stenosis (RAS) is typically due to either fibromuscular dysplasia or atherosclerotic lesions. Fibromuscular dysplasia has a prevalence of ~0.4% in the general population and is most commonly seen in women 20 to 50 years old. Screening for fibromuscular dysplasia should be considered in women younger than 50 years with recent onset of RH. Computed tomography angiography is preferred over magnetic resonance angiography because the lesions are distal and better visualized on computed tomography angiography. If a symptomatic lesion is detected, it is best treated with percutaneous angioplasty and stenting is rarely needed.

Atherosclerotic disease is increasingly prevalent with age. A recent study showed that 24% of elderly patients with RH had significant RAS. Revascularization may lower BP in patients with RAS and uncontrolled RH. Following medication optimization, patients with uncontrolled RH who lack other causes of secondary hypertension may be screened for significant stenosis with duplex ultrasonography of the renal arteries. Use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is safe in unilateral and bilateral RAS, confers mortality benefit, and is a component of optimal therapy.

Three recent trials of routine renal angioplasty and stenting were shown to confer no additional benefit beyond optimal medical therapy in patients with stable CKD. Routine screening for RAS in the setting of CKD is therefore discouraged and should only be pursued in patients who have a high likelihood of benefitting from intervention because these patients were excluded from these trials. Such patients include those with a solitary kidney, severe RH, recurrent episodes of “flash pulmonary edema,” refractory heart failure, recurrent acute kidney injury following the introduction of ACE inhibitor or ARB therapy, or otherwise unexplained progressive decreases in kidney function.

Pheochromocytoma/Paraganglioma
Chromaffin cell tumors have an increased prevalence in patients with RH and testing should be considered based on clinical symptoms. Most patients have elevated BP, but only one-half experience paroxysmal hypertension. The “classic triad” of episodic headache, sweating, and tachycardia are present in a minority of patients, although each symptom is common. Plasma free metanephrine level is the best screening test; it has high sensitivity and specificity and, unlike measurement of fractionated metanephrines, does not require 24-hour urine collection. Metanephrine levels are approximately 2 to 3 times higher than the usual upper limit of normal in patients with stage 4-5 CKD and those receiving dialysis. Further evaluation and management of positive test results should follow the Endocrine Society clinical practice guidelines and prompt referral to a center with clinical expertise.
Other Causes of Secondary Hypertension

Other endocrine disorders may rarely cause secondary hypertension, including Cushing syndrome, hyper- and hypothyroidism, and syndromes of excess deoxycorticosterone. A concise workup for secondary hypertension is shown in Table 1.

Treatment

Management of RH begins with lifestyle interventions. Dietary sodium restriction, weight loss, heart-healthy diet (eg, Dietary Approaches to Stop Hypertension [DASH]), increased physical activity, and reduced alcohol consumption all have high-quality evidence to support their recommendation in the management of hypertension and are routinely recommended to patients with RH. However, DASH-style diets and reduced alcohol consumption (<10 g/d in women and <20 g/d in men) have yet to be studied specifically in RH. The combined effect of multiple lifestyle interventions for RH has the potential to substantially reduce BP and is being evaluated in the TRIUMPH trial, projected to complete in November 2020 (ClinicalTrials.gov identifier, NCT02342808).

Sodium Restriction

Dietary sodium restriction can profoundly decrease BP in patients with RH with or without CKD. Decreasing sodium intake by 1 g/d reduces Systolic BP by 2.1 mm Hg. AHA and KDOQI guidelines recommend <2.4 g/d (<100 mmol/d) of sodium intake, but limiting sodium consumption to recommended levels outside a controlled setting is challenging because even a “no added salt” diet typically contains 4 g/d of sodium. A “low protein” diet may augment BP reduction due to increased selection of low-sodium foods.

Dietary Potassium Supplementation

Diet rich in potassium (eg, DASH) reduce BP but are not recommended in moderate to severe CKD until further studies demonstrate safety.

Physical Activity

Multiple clinical trials have shown that exercise (30 minutes of moderate-intensity physical activity ≥5 days per week) effectively lowers BP. A randomized controlled trial evaluating a treadmill exercise program in RH showed a BP reduction of 6/3 mm Hg measured using ABPM.

Table 1. Evaluation of Secondary Hypertension

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Suggestive Clinical Features</th>
<th>Screening Tests</th>
<th>Confirmatory Tests</th>
<th>Considerations in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary aldosteronism</td>
<td>Hypokalemia; metabolic alkalosis; adrenal incidentaloma; HTN onset at young age</td>
<td>PRA, PAC</td>
<td>24-h urine aldosterone or saline suppression testing; if positive proceed with AVS</td>
<td>High suspicion in CKD patient with RH and hypokalemia on RAAS blockade</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Scr increase &gt;50% on ACEi/ARB; diffuse atherosclerotic disease; flash pulmonary edema; females &lt;50 y with recent-onset RH</td>
<td>Renal artery duplex ultrasonography</td>
<td>CTA (preferred initial study when suspecting FMD) or MRA</td>
<td>Not a contraindication to ACEi/ARB therapy</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal HTN; triad of headache, palpitations, and diaphoresis</td>
<td>Fractionated plasma metanephrines</td>
<td>Adrenal/abdominal MRI or CT</td>
<td>Plasma metanephrines may be 2-3× the upper limit of normal in CKD4-5 or dialysis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Heat intolerance; nervousness; insomnia; diarrhea; weight loss</td>
<td>TSH, T3, fT4</td>
<td>Radioactive iodine uptake and scan</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Dry skin; cold intolerance; constipation; weight gain</td>
<td>TSH, fT4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Obesity; facial plethora; proximal myopathy; purple striae; easy bruising; diabetes</td>
<td>Late-night salivary cortisol, 24-h urinary free cortisol, overnight DST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid excess syndromes</td>
<td>Early-onset HTN; hypokalemia</td>
<td>PRA, PAC</td>
<td>DOC; urinary cortisol metabolites; genetic testing</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVS, adrenal vein sampling; CKD, chronic kidney disease; CT, computed tomography; CTA, computed tomography angiography; DOC, deoxycorticosterone; DST, dexamethasone suppression test; FMD, fibromuscular dysplasia; fT4, free thyroxine; HTN, hypertension; MRA, magnetic resonance angiography; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; RH, resistant hypertension; Scr, serum creatinine; T3, triiodothyronine; TSH, thyroid-stimulating hormone. Based on information in Carey et al.
Weight Loss

Weight loss reduces BP by 0.6 to 1.0 mm Hg per kilogram of weight lost. Comprehenscive programs that include behavioral modification with diet and exercise programs improve the likelihood of sustained weight loss and should be offered to patients with body mass index ≥ 25 kg/m² and hypertension.

When weight loss goals are unmet, pharmacologic intervention may be recommended; however, additional considerations are appropriate in patients with RH or CKD. In particular, orlistat can precipitate calcium oxalate nephrolithiasis, lorcaserin is contraindicated at eGFR < 30 mL/min/1.73 m², and sympathomimetics can exacerbate hypertension.

Bariatric surgery can be beneficial for BP management and should be considered for patients who do not meet weight loss goals despite intensive therapy. A recent randomized trial in patients with obesity and hypertension but without CKD evaluated the BP-lowering effect of combined medical management and Roux-en-Y gastric bypass. Compared with medical management alone, patients treated with Roux-en-Y gastric bypass had significant reduction in the number of antihypertensives required to meet BP goals. A further substudy of trial participants with RH found that the prevalence of apparent RH decreased in patients randomly assigned to Roux-en-Y gastric bypass.

Pharmacologic Treatment

A proposed algorithm to the diagnosis and initial management of RH is shown in Figure 1. Suboptimal medication regimens are common in RH and pharmacotherapy is initially directed toward improving existing BP medications and simplifying dosing. Hydrochlorothiazide should be switched to indapamide or chlorthalidone. If loop diuretics are used, once-daily torsemide is preferred. Recent studies suggest that valsartan and irbesartan are less potent than other ARBs, and adjustments to ACE inhibitor/ARB therapy may also be necessary.

Patients with RH who do not meet diagnostic criteria for PA often respond to aldosterone antagonists. PATHWAY-2 was a large, multicenter, randomized, double-blind, placebo-controlled, crossover trial comparing 12 weeks each of spironolactone, doxazosin, bisoprolol, and placebo in random order as four-line agents in patients with RH receiving standard 3-drug regimens of an ACE inhibitor/ARB, a calcium channel blocker, and diuretic. Spironolactone was by far superior to placebo and the 2 other active treatments. Compared with placebo, spironolactone reduced home SBP by 8.70 mm Hg and an additional 5 to 6 mm Hg compared with the other agents. The benefit of spironolactone was greatest in patients with suppressed renin levels but remained superior across all serum renin concentrations. Titration of spironolactone from 25 to 50 mg daily showed additional BP reduction. In patients who were unable to tolerate spironolactone, amiloride showed similar efficacy as a fourth-line agent. All active treatments were well tolerated with similar low rates of adverse events. Discontinuation of spironolactone therapy due to decreased kidney function, hyperkalemia, or gynecomastia was no more frequent with spironolactone versus other medications.

Figure 1. Evaluation and management of resistant hypertension (RH). Not recommended in moderate to severe chronic kidney disease (CKD). Abbreviations: 2°, secondary; ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; HR, heart rate; HTN, hypertension; OSA, obstructive sleep apnea.
treatments or placebo. All active drugs that lowered BP decreased eGFR, though it was not deemed clinically relevant. Only 6 of 285 patients exposed to spironolactone developed a serum potassium level > 6.0 mmol/L, and the maximum value was 6.5 mmol/L. This is an important study that has clearly established spironolactone as the most effective fourth-line agent for the treatment of RH.

In patients with CKD, the combination of spironolactone and ACE inhibitor/ARB therapy doubles the risk for hyperkalemia and drug cessation. AMBER was a phase 2, multicenter, randomized, double-blind, placebo-controlled study of 295 patients with RH and eGFR of 25 to 45 mL/min/1.73 m². Patients remained on their baseline of 3 or more BP medications including a diuretic and an ACE inhibitor/ARB (unless not tolerated or contraindicated). Patients were randomly assigned to spironolactone in addition to either placebo or patiromer. At week 12, a total of 66% of 148 patients in the placebo group and 86% of 147 patients in the patiromer group remained on spironolactone therapy (between-group difference, 19.5% [95% confidence interval, 10.0-29.0]; P < 0.0001). Significant reductions of ~11 mm Hg in SBP from baseline to week 12 occurred in both treatment groups. The most common adverse event was hyperkalemia, with 9% in the placebo group and 6% in the patiromer group. Overall, two-thirds of patients in the placebo group developed hyperkalemia and this risk was halved in the patiromer group. Of patients in the patiromer and placebo groups, 69% and 51%, respectively, were uptitrated to 50 mg of spironolactone. This study demonstrated that using a potassium binder (patiromer) in patients with RH with significantly reduced eGFR enables more patients to continue treatment with spironolactone with less hyperkalemia and potentially improved BP control.

Recommendations regarding further additions to medical management are expert opinion. The observation that hypertensive patients with increased heart rates (>80 beats/min) have higher mortality suggests that β-blockers should be considered in patients who are not bradycardic. Direct vasodilators, α-blockers, and central α₂-agonists are therapies that are used less frequently when there is intolerance of other agents. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have not been studied for the treatment of RH but recent trials in CKD and heart failure populations have shown modest BP reduction in the range of 4/2 mm Hg. SGLT2 inhibitors may be particularly important in patients with CKD and RH considering their impressive reductions in cardiovascular outcomes, heart failure, and the progression of CKD. Endothelin A receptor antagonists, vasopeptidase inhibitors, and aminopeptidase A inhibitors are other novel agents currently being evaluated in the treatment of RH.

**Devices for RH**

Sympathetic nervous system (SNS) tone is an important factor in the development of hypertension and CKD. Recently, device-based interventions targeting the SNS have been investigated as BP-lowering therapies. A summary of completed trials is included in Table 2.

**Renal Denervation**

Renal efferent SNS signaling increases renin release and tubular sodium reabsorption. Catheter-based renal denervation (RDN) was developed to intervene in this pathway, and initial trials in patients with RH were promising. However, the SIMPLICITY-HTN-3 trial failed to show superiority in BP reduction with RDN compared with the sham procedure. Although there were several concerns regarding patient selection, procedure execution, and medication regimens in SIMPLICITY-HTN-3, studies that favored RDN, including DENER-HTN, have been criticized as well for unblinded design and lack of sham procedures. A small number of nonrandomized clinical trials using RDN in CKD have shown promising results. Recent sham-controlled randomized studies have shown BP reduction in less severe hypertension similar to what one would expect with a single antihypertensive agent. More comprehensive data are still pending for those with more severe hypertension. It is unclear which patients have a more robust BP response, but some studies indicate that those with higher SBPs have greater response. Current evidence is insufficient to support the use of RDN in RH until ongoing trials are completed (ClinicalTrials.gov identifiers NCT02439775 and NCT02649426).

**Baroreceptor-Directed Therapies**

Baroreceptors in the aortic arch and carotid sinuses are essential for SNS and cardiovascular regulation. Carotid sinus nerve stimulation has been attempted with multiple implanted devices and a recent pooled analysis of an electrical device showed significant decreases in office BP (by 35/18 mm Hg), although there were high rates of surgical complications. A unilateral endovascular implant that sits within the internal carotid artery, changing the geometric shape of the baroreceptor and thereby amplifying its inhibitory function, has been studied and showed significantly lowered BP in patients with RH. A prospective sham-controlled trial is currently on hold due to poor enrollment (ClinicalTrials.gov identifier NCT03179800).

**Summary**

RH has been redefined as BP that has been confirmed by out-of-office BP measurement to exceed the individualized BP target despite adherence to at least 3 maximally dosed antihypertensives, ideally including a diuretic. The prevalence of true RH is unknown and is likely lower than reported, but more common in patients with CKD. Evaluation of patients with apparent treatment resistance includes an assessment of and reduction in barriers to medication adherence. Screening for PA is a necessary step in evaluation, and other causes of secondary hypertension...
should be considered. Treatment of RH begins with addressing lifestyle factors that contribute to disease resistance, including interfering medications, dietary sodium intake, physical activity, obesity, and OSA. For patients with CKD, escalation of diuretic therapy is essential for BP reduction in patients who are volume expanded. When a fourth-line antihypertensive is necessary, aldosterone antagonists are preferred. Novel therapeutic devices need additional exploration before routine use in clinical practice.

**Table 2. Completed Trials of Devices for the Treatment of Resistant Hypertension**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Inclusion Criteria</th>
<th>Randomized</th>
<th>Blinded</th>
<th>Sham Control</th>
<th>F/U</th>
<th>Result</th>
<th>Criticisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPLICITY HTN-1</td>
<td>RDN</td>
<td>Apparent RH</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>3 y</td>
<td>Avg BP decline, 32/14 ± 4/2.5 mm Hg</td>
<td>Not randomized</td>
</tr>
<tr>
<td>SYMPLICITY HTN-2</td>
<td>RDN</td>
<td>Apparent RH</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>6 mo</td>
<td>Avg BP decline, 33/14 ± 7/4 mm Hg</td>
<td>Non-optimal medical therapy and no sham control</td>
</tr>
<tr>
<td>SYMPLICITY HTN-3</td>
<td>RDN</td>
<td>True RH</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6 mo</td>
<td>No superiority over sham</td>
<td>Inadequate pt selection; poor operator experience; poor technical performance of procedure</td>
</tr>
<tr>
<td>DENERHTN</td>
<td>RDN</td>
<td>Apparent RH</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>6 mo</td>
<td>Significantly reduced SBP vs medical therapy alone</td>
<td>Poor medication adherence</td>
</tr>
<tr>
<td>DEBuT-HTN</td>
<td>Electrical BAT</td>
<td>True RH</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2 y</td>
<td>Avg BP decline, 24/13 ± 8/5 mm Hg</td>
<td>Surgical complications were common</td>
</tr>
<tr>
<td>Rheos Pivital</td>
<td>Electrical BAT</td>
<td>True RH</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>6 mo</td>
<td>Intervention did not meet predefined efficacy for SBP (≥10 mm Hg decline)</td>
<td></td>
</tr>
<tr>
<td>CALM-FIM_EUR</td>
<td>Endovascular baroreflex amplification therapy</td>
<td>True RH</td>
<td>No</td>
<td>No</td>
<td>6 mo</td>
<td>Avg BP decline, 21/12 ± 7/4 mm Hg</td>
<td>High rate of adverse events</td>
<td></td>
</tr>
<tr>
<td>ROX CONTROL-HTN</td>
<td>Arteriovenous shunt</td>
<td>True RH</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1 y</td>
<td>Statistically significant BP decline vs medical therapy alone</td>
<td>High rate of venous stenosis requiring intervention</td>
</tr>
</tbody>
</table>

**Abbreviations:** BAT, baroreceptor activation therapy; BP, blood pressure; F/U, follow-up; pt, patient; RDN, renal denervation; RH, resistant hypertension; SBP, systolic blood pressure.

**References**

medications for patients with uncontrolled blood pressure: still no better than a coin toss. BMC Health Serv Res. 2012;12:270.
75. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and


