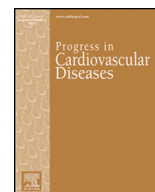




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The management of resistant hypertension: A 2020 update

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ABSTRACT

Resistant hypertension (RH) induces higher morbidity and mortality due to cardiovascular disease and stroke than hypertension without treatment resistance. New guidelines define RH as blood pressure (BP) $\geq 130/80$ mmHg in a patient taking ≥ 3 antihypertensive agents of different classes or BP $< 130/80$ mmHg in a patient taking ≥ 4 antihypertensive drugs. According to the new definition, pseudo-resistance due to error in BP measurement, white coat effect and medication nonadherence must be excluded to make the diagnosis of RH. This 2020 update focuses on the lifestyle and antihypertensive drug management of RH and includes recent proof-of-principle trials of renal nerve ablation in hypertension. Stepwise evidence-based pharmacologic treatment of RH includes optimization of the 3-drug regimen, substitution of a thiazide-like for a thiazide diuretic and addition of a mineralocorticoid receptor antagonist as the fourth drug. Non-evidence-based recommendations include addition of a β -blocker as the fifth drug and switching to a minoxidil-based regimen as the final step in achieving BP control.

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Abbreviations: ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; ACEI, angiotensin converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARR, aldosterone:renin ratio; aTRH, apparent treatment resistant hypertension; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DENERHTN, The Renal Denervation for Hypertension; eGFR, estimated glomerular filtration rate; HBPM, home blood pressure monitoring; LA, long-acting; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; PATHWAY-2, Prevention and Treatment of Hypertension with Algorithm Based Therapy-2; RH, resistant hypertension; SBP, systolic blood pressure; SIMPLICITY HTN-3, SIMPLICITY™ Hypertension-3; SPYRAL-OFF MED, Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy; TRIUMPH, Treating Resistant Hypertension Using Lifestyle Modification to Promote Health.

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Introduction

Resistant hypertension (RH) is defined as the blood pressure (BP) of a hypertensive patient that remains uncontrolled above goal in spite of the concurrent use of three antihypertensive drugs of different classes.¹ These pharmacologic classes usually include a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system [angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)] and a diuretic. All three antihypertensive agents must be prescribed at maximum or maximally tolerated doses and at the appropriate dosing interval. The term RH also applies to patients whose BP is controlled below goal, but requires four or more antihypertensive agents of different classes to achieve the target.¹ Thus, the term RH applies to hypertension with BP that is either controlled or uncontrolled, depending on the number of antihypertensive agents employed.¹ The definition of RH is summarized in Fig. 1.

Before the diagnosis of RH can be confirmed, pseudo-resistance must be excluded. Pseudo-resistance refers to a patient whose BP and number of antihypertensive medications meets the definition of RH, but one or more interfering conditions is present which allows the hypertension to masquerade as RH. In order of the usual diagnostic sequence, these conditions include: (1) error in BP measurement; (2) the “white coat effect”; and (3) suboptimal adherence or non-adherence to the antihypertensive drug regimen. Prior to the 2018 American Heart Association (AHA) Scientific Statement on resistant hypertension,¹ individuals who fit the BP and antihypertensive drug criteria for RH but also had one of these four conditions were considered as having apparent treatment RH (aTRH). Now, however, these conditions that interfere with the diagnosis (Fig. 2) must be excluded before labeling a patient as having RH.¹

Accurate BP measurement is the cornerstone in the diagnosis of RH. However, failure to measure BP accurately is unfortunately all too common. The preparation of the patient, environmental conditions, cuff size and technique of BP measurement all have profound effects on BP readings and the classification of high BP and RH.² Detailed guidelines for the

SEPARATE TRUE- FROM PSEUDO- RESISTANT HYPERTENSION

The definition of resistant hypertension requires:

- Accurate blood pressure measurement according to current guidelines (references 2 & 3)
- Exclusion of the “white coat effect” using ambulatory blood pressure monitoring (ABPM) or, if unavailable, home blood pressure monitoring (HBPM)
- Exclusion of suboptimal medication adherence or medication non-adherence

Fig. 2. Exclusion of the causes of pseudo-resistance in the diagnosis of resistant hypertension. ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring.

proper measurement of BP in the medical office and at home have recently been published.^{2,3} Common errors in BP measurement are displayed in Fig. 3. One or more of these errors often increase BP and are especially common in aTRH. Because BP is intrinsically variable, BP classification, including the designation of RH, requires a minimum of 2 readings on at least 2 different occasions.³

The “white coat effect” is defined as office BP above goal but out-of-office BP, preferably measured by ambulatory BP monitoring (ABPM) but, if unavailable, home BP monitoring (HBPM), at or below goal in a patient taking antihypertensive drug therapy.^{1–3} The risk of cardiovascular disease (CVD) events in a patient with the white coat

CONFIRM TREATMENT RESISTANCE

Uncontrolled Resistant Hypertension

- Office BP $\geq$ 130/80 mmHg and/or 24 hour ambulatory BP $\geq$ 125/75 mmHg
- Patient taking $\geq$ 3 antihypertensive agents of different classes
Most commonly including:
A long-acting calcium channel blocker
A renin-angiotensin system blocker (ACE inhibitor or ARB)
A diuretic

All at maximal or maximally tolerated doses

- Pseudo-resistance excluded

Controlled Resistant Hypertension

- Office BP < 130/80 mmHg and/or 24 hour ambulatory BP < 125/75 mmHg
- Patient taking $\geq$ 4 antihypertensive agents of different classes
- Pseudo-resistance excluded

Fig. 1. Definition of resistant hypertension. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure.

COMMON ERRORS IN OFFICE BLOOD PRESSURE MEASUREMENT

- Not allowing the patient to rest in a quiet area for at least 5 minutes prior to measurement
- Not having the patient empty their bladder prior to measurement
- Measuring blood pressure with the patient on the examining table with back unsupported
- Measuring blood pressure while the patient is standing or supine
- Measuring blood pressure with the arm unsupported at heart level
- Engaging the patient in conversation during the blood pressure measurement
- Using a blood pressure cuff that is too small for the diameter of the arm
- Placing the blood pressure cuff over clothing
- Introducing digital bias through use of nonautomated devices

Fig. 3. Common errors that increase blood pressure leading to a diagnosis of resistant hypertension in patients without true resistant hypertension.

effect is similar to the risk in hypertensive patients with controlled BP.^{4–6} While out-of-office BP monitoring is required to detect the white coat effect, this diagnosis is critical, as designation of the white coat effect mitigates against upward titration of antihypertensive medication number/dose in patients with RH who are uncontrolled by office BP measurements.

Before the diagnosis of RH can be confirmed, adherence to the antihypertensive drug regimen must be assured. Medication nonadherence is extremely common in patients with aTRH, as indicated by the 50–80% of hypertensive patients prescribed antihypertensive drugs who demonstrate suboptimal adherence.^{7–10} This is likely related to a multiplicity of factors, including large pill burden, dosing complexity, expense, high frequency of adverse side effects, inadequate patient-clinician interaction and clinician inertia (failure to insist on adherence when the patient is known to be consistently nonadherent).¹¹ Exclusion of nonadherence (for methods see Fig. 4) should include frank and non-judgmental discussion with the patient, monitoring of prescription refills and pill counts, and, when possible, biochemical monitoring of drugs or their metabolites in urine or plasma (therapeutic drug monitoring).¹

AVAILABLE METHODS OF ANTIHYPERTENSIVE DRUG MONITORING

INDIRECT METHODS	DIRECT METHODS
Self-report Questionnaire (eg. Morisky Medication Adherence Scale) Diary Interview	Witnessed drug intake Directly observed therapy
Pill count Manual Electronic monitoring device (eg. pill box) Prescription registries	Therapeutic drug monitoring Spot blood or urine sample analysis (HPLC/MS)

Fig. 4. Direct and indirect methods of monitoring medication adherence in hypertensive patients. HPLC/MS, high pressure liquid chromatography/mass spectrometry.

Another situation that merits attention is the possibility that BP is controlled with antihypertensive medication in the office but is uncontrolled in out-of-office measurements. This circumstance, known as masked uncontrolled hypertension, carries a prognosis that is at least as detrimental as that of uncontrolled sustained hypertension. If the patient is taking 3 antihypertensive medications of different classes and has controlled BP in the office but uncontrolled readings out-of-office, the patient has masked RH. Although no randomized controlled trial data are currently available on the benefit of treatment escalation either in masked hypertension or masked RH, prudence dictates that this condition should be treated similarly to uncontrolled RH.

Because the 2017 ACC (American College of Cardiology)/AHA hypertension clinical practice guideline redefined the general BP goal for hypertensive adults as <130/80 mmHg (systolic BP goal < 130 mmHg in adults ≥ age 65 years), the definition of RH has changed from its previous cutoff level of BP ≥ 140/90 mmHg (≥130/80 mmHg in diabetes mellitus and chronic kidney disease) to ≥130/80 mmHg for all patients on ≥ three antihypertensive medications of different classes^{1,3} (Fig. 1). Although many experts expected this change in the definition of RH to markedly increase the prevalence of RH, placing an undue burden on the health care system, population modeling studies indicate that this change will result in only about a 2% increase in prevalence of RH (from 17.7 to 19.7%) in the United States.¹² It is also important to note that while the new goal for BP control in the office is <130/80 mmHg, BP control by 24-h ABPM is now <125/75 mmHg according to the 2017 ACC/AHA hypertension guideline; this ABPM cutoff value was recently validated.^{3,13}

RH is an important designation because it is associated with a higher prevalence of target organ damage and worse CVD prognosis than in non-RH patients with hypertension.^{1,14,15} This update focuses on the management of RH with emphasis on its medical treatment. Because concomitant non-pharmacologic treatment is a critical factor in promoting the success of drug therapy, lifestyle management is also briefly covered. Although device-based therapy for RH remains experimental at present, some interesting recent proof-of-principle studies in patients with hypertension without treatment resistance will be reviewed. Thus, renal denervation using newer device-based techniques may be possible for selected (eg. nonadherent) patients with RH in the future.

Drug-induced and secondary hypertension

Several classes of pharmacologic agents can raise BP and cause or worsen RH¹. These include nonsteroidal anti-inflammatory agents (NSAIDs), oral contraceptives and ovarian hormone replacement therapy in women, sympathomimetic amines, immunosuppressive agents (eg. cyclosporine, tacrolimus), recombinant human erythropoietin, tyrosine kinase inhibitors, cocaine, amphetamines, and antidepressants. It must be emphasized that there is high variability in BP responses to these agents. Some individuals show little or no effect, while others can have a major increase in BP that leads to or aggravates RH. In patients with RH taking these agents, systematic withdrawal, when possible, can reduce BP and even eliminate RH in some patients.

RH is a common manifestation of certain forms of secondary hypertension (Fig. 5), most prominently primary aldosteronism and the pheochromocytoma/paraganglioma syndrome. The diagnosis of RH requires screening for both of these disorders, as well as renal parenchymal disease and renal artery stenosis (if BP is unable to be controlled medically and/or significant deterioration in renal function occurs).¹ Primary aldosteronism has a prevalence of about 8% in adults with hypertension; prevalence increases to about 20% in RH. Although all patients with RH should be screened for primary aldosteronism, recent cohort studies demonstrate that only 2.1% of adults with RH are screened.¹⁶ Recent studies document an even larger proportion of unrecognized primary aldosteronism among patients thought to have primary hypertension and RH, and even among the normotensive population.^{17,18} Screening for primary aldosteronism currently consists of the plasma aldosterone/plasma renin activity ratio [aldosterone:renin ratio (ARR)], the blood sample for which should be obtained in the morning with the patient in the seated position after correction of hypokalemia [serum K⁺ ≥ 3.5 mmol/L after oral potassium chloride supplementation and in the absence of mineralocorticoid receptor antagonist (spironolactone or eplerenone) therapy for 5–6 weeks].¹⁸ Screening for pheochromocytoma/paraganglioma requires plasma free metanephrines (metanephrine and normetanephrine) or, alternatively, 24-h fractionated urine metanephrine excretion rate.¹⁹ Renal disease as a cause of secondary hypertension can be screened with an estimated glomerular filtration rate (eGFR). Renal artery stenosis can be screened using duplex ultrasonography to identify increased peak systolic velocity in the renal arteries; this is commonly confirmed using magnetic

resonance arteriography or computerized tomography angiography. Uncommon secondary causes of RH are virtually all endocrine and include Cushing's syndrome, hypo- or hyper-thyroidism, primary hyperparathyroidism, uncommon varieties of congenital adrenal hyperplasia (eg. 11-β hydroxylase deficiency and 17-α hydroxylase deficiency), other rare corticosteroid excess syndromes, and acromegaly.¹ Because these disorders are often difficult to evaluate, confirm and manage, detection of a specific disorder causing secondary hypertension by screening in most cases should prompt referral to a hypertension specialist, endocrinologist or nephrologist, as appropriate. While obstructive sleep apnea has been considered by some authorities as a secondary form of RH, treatment with continuous positive airway pressure (CPAP) results in only modest (2–3 mmHg) BP reduction and does not prevent CVD events in randomized controlled trials.^{1,20}

Lifestyle interventions

As with the prevention and treatment of hypertension in general, the 2018 AHA Scientific Statement on RH recommends broad lifestyle changes, when appropriate and feasible, including weight loss, regular exercise, reduction of dietary sodium intake, augmentation of dietary potassium intake, moderation of alcohol consumption and healthy sleep pattern.¹

While the efficacy and safety of lifestyle modifications (Fig. 6) are generally well established for the treatment of hypertension, the specific demonstration of antihypertensive benefit, feasibility and tolerability in patients with RH is severely limited. This situation is expected to be remedied when the results of a randomized controlled trial [Treating Resistant Hypertension Using Lifestyle Modification to Promote Health (TRIUMPH) trial, initiated in 2015] testing the effectiveness and safety of a variety of lifestyle modifications specifically in RH are reported.²¹ While the challenges of having patients initiate and especially maintain meaningful lifestyle modifications are widely recognized, the 2018 AHA Scientific Statement broadly encourages lifestyle modification in RH, not only to enhance BP control but also to improve overall cardiovascular health in this high-risk hypertensive subpopulation.¹ Due to limitations of time and expertise in busy medical practice, lifestyle counseling should optimally be performed in most practices by specifically educated and trained paramedical personnel, such as lifestyle counselors.

SCREENING FOR SECONDARY CAUSES OF RESISTANT HYPERTENSION

SECONDARY CAUSE	SCREENING METHOD
Primary aldosteronism*	ARR in the seated position in the morning (serum K ⁺ ≥ 3.5 mmol/L; no MRA for 5-6 weeks)
Pheochromocytoma/ paraganglioma**	Plasma free metanephrines or 24-h fractionated urine metanephrines
Chronic kidney disease*	eGFR
Renal vascular hypertension*	Duplex US (or MR arteriogram or CTA)
Cushing's syndrome	Overnight 1 mg dexamethasone suppression test
Hypo- or hyperthyroidism	TSH and free T4
Hyperparathyroidism	Serum calcium and PTH concentration
Acromegaly	Serum IGF-1 level

Fig. 5. Causes of secondary hypertension leading to treatment resistance. *Screening based on relatively common occurrence in resistant hypertension. **Screening based on high morbidity and mortality if remains undetected. ARR, aldosterone:renin ratio; CTA, computerized tomography arteriography; eGFR, estimated glomerular filtration rate; IGF-1, insulin growth factor-1; MR, magnetic resonance; MRA, mineralocorticoid receptor antagonist; PTH, parathyroid hormone concentration; US, ultrasound.

LIFESTYLE MODIFICATION FOR RESISTANT HYPERTENSION

INTERVENTION	IMPLEMENTATION/GOAL	RCT Evidence in RH
Dietary sodium restriction	<1500 mg/day; mainly reduced processed food	Yes
Healthy diet.	DASH dietary pattern	No
Dietary potassium supplementation	3,500-5,000 mg/day, preferably as dietary constituents	No
Weight loss	Ideal BMI	No
Exercise	90-150 min/week	Yes
Healthy sleep pattern	8 h/night uninterrupted sleep.	Yes

Fig. 6. Nonpharmacological treatment, treatment goals and presence of trial-based evidence in resistant hypertension. BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; RCT, randomized controlled trial; RH, resistant hypertension.

Here we will briefly cover the lifestyle modifications recommended for all adults with elevated BP, stages 1 and 2 hypertension and RH, and will highlight the small number of randomized controlled trials, which are generally small and underpowered, in patients with RH.

Weight loss

Obesity is a strong determinant of hypertension.^{1,22,23} In overweight individuals with hypertension, one can expect about a 1 mmHg reduction in SBP for every kg of weight loss. The best weight goal is ideal body weight, but overweight adults with hypertension are advised to lose at least one kg. Weight reduction can provide an average BP reduction of about 5 mmHg in overweight adults with hypertension.¹ No randomized clinical trials are yet available to judge the effectiveness of weight loss on BP in RH. However, it is safe to assume that weight loss augments the hypotensive response to drug therapy.

Dietary sodium restriction

The American diet contains very large quantities of sodium, with the average American consuming 3400 mg per day, far in excess of current dietary recommendations that limit daily sodium intake to 2300 mg or less for all Americans. The ACC/AHA hypertension guideline advises an optimal sodium intake goal, if possible, of <1500 mg sodium daily, but recommends a minimum 1000 mg/day reduction in most adults with hypertension.³ Reducing sodium intake to this extent in adults with hypertension is effective in lowering SBP by an average of 5–6 mmHg, a similar reduction as provided by antihypertensive drug monotherapy.³

The benefit of dietary sodium restriction specifically in patients with RH has only been demonstrated in 2 small studies (12 and 20 patients, respectively) in patients with RH and/or CKD.^{24,25} However, both of these studies demonstrated dramatic effects on BP, including a reduction of 23/9 mmHg in 24-h ambulatory BP during 4 weeks of 1000 mg sodium per day versus 5700 mg/day sodium intake in the controls.²¹ Although results of larger clinical trials in diverse populations are not yet available, it is highly likely that dietary sodium restriction lowers BP and augments the antihypertensive response to drugs in RH. Therefore, dietary sodium reduction in RH is strongly endorsed as a complement of pharmacologic therapy.

Dietary potassium supplementation

Potassium intake is inversely related to BP and potassium supplementation lowers BP in randomized trials, but no studies on the effects of potassium supplementation are currently available for RH. For hypertension in general, 3500–5000 mg potassium per day are

recommended, preferably as dietary constituents rather than pill-based supplements. This level of dietary potassium intake can reduce SBP by an average of 4–5 mmHg in hypertensive adults. The effect is particularly striking in individuals consuming a high sodium intake.³

Dietary approaches to stop hypertension (DASH) diet

The DASH diet is a key therapeutic intervention that promotes BP control. Because the DASH diet is rich in fruits, vegetables, fiber and low-fat dairy products, it promotes potassium, calcium and magnesium supplementation. Among all lifestyle modifications, the DASH diet provides the most significant SBP reduction in hypertensive adults (average minus 11 mmHg).³ When combined with sodium restriction and/or weight loss, the effects on BP are additive. While other diets, such as the Mediterranean diet and vegetarian or vegan diets lower BP, the DASH diet is best demonstrated to lower BP in hypertension. While no DASH diet trials are available in RH, the DASH diet plan would be expected to lower BP and augment the effects of other lifestyle changes as well as pharmacologic therapy in RH.

Exercise

Exercise, both aerobic and anaerobic, is well recognized to lower BP.²³ Between 90 and 150 min per week of aerobic exercise reduces SBP by 5–8 mmHg in hypertensive patients; a similar amount of dynamic or static isometric resistance exercise lowers SBP by about 4–5 mmHg over an 8–10 week period.²⁶ The antihypertensive benefit and safety of monitored exercise programs in patients with RH have been demonstrated in 2 small studies, one in a treadmill walking exercise program and the other in a water-based exercise program.^{27,28}

Limitation of alcohol consumption

A strong and predictable relationship exists between alcohol consumption and BP, particularly at ≥ 3 drinks per day and meta-analysis of randomized trials in hypertensive adults shows consistent BP lowering with restriction of alcohol intake below this level. For this reason, guidelines recommend limitation of alcohol consumption to ≤ 1 standard drink per day for women and ≤ 2 standard drinks per day for men.³ On average, this should result in about a 4 mmHg reduction of SBP in adults with hypertension. There is a striking absence of clinical trials of alcohol withdrawal in RH, but logic would dictate that the general recommendations for limitation of alcohol consumption should apply in RH.

Healthy sleep pattern

Improving sleep duration and quality is recommended to reduce BP based on a growing body of literature relating short sleep duration to both higher rates of incident and prevalent hypertension in general, as well as in a small number of studies that have specifically evaluated patients with RH.¹ Recently, a small pilot study in patients with CKD, RH and poor sleep quality or sleep duration <6 h per night demonstrated a highly significant reduction in SBP from 156 to 125 mmHg over a 6 month period of improved sleep hygiene and/or sleep medication with 8 h of sleep per night.²⁹

Pharmacologic interventions

Once the patient has met the diagnostic criteria for RH (with pseudo-RH excluded), a set of pharmacologic interventions should occur in stepwise fashion, as indicated below.

Step 1: Optimization of the 3-drug regimen

Optimization of the three drug antihypertensive regimen is an imperative first step in pharmacologic treatment. The three drug regimen combines pharmacologic classes (CCB, ACEI or ARB, and thiazide diuretic) with complementary mechanisms of action that are effective both individually and in combination to lower BP and prevent CVD. The drugs should be administered at maximal (Table 1) or maximally tolerated doses; examples include calcium channel blocker amlodipine 10 mg daily, thiazide diuretic hydrochlorothiazide 25–50 mg daily and an ACEI or ARB at maximal dose. All of the agents recommended in the three drug regimen are available as generic and long-acting formulations and as dual or triple pill combinations and are generally well tolerated.

CCBs are an important component of the three drug regimen. Dihydropyridine CCBs such as amlodipine and long acting nifedipine (nifedipine LA) are the best studied and most widely employed CCBs in hypertension and RH. Non-dihydropyridine CCBs such as verapamil

may also be helpful, but are less well established in RH and are contraindicated in patients with coexisting heart failure with reduced ejection fraction.

The choice of an ARB may be important, as the wide variety of available ARBs each have different pharmacological properties (i.e. receptor selectivity, insurmountability, inverse agonist properties, β -arrestin-1-dependent aldosterone production) and studies comparing their ability to lower BP demonstrate clear advantages of some ARBs over others. For example, azilsartan medoximil, the newest available ARB, provides further BP reduction (4–5 mmHg) over valsartan or olmesartan or the ACEI ramipril.^{30–32}

The time of dosing may also be important. Administering one or more of the drugs in the triple drug regimen at night may improve BP control. However, diuretics should generally be administered in the morning to avoid nocturnal diuresis disrupting sleep. Also, using divided doses of drugs with half-lives <12–15 h may improve BP control even though the drug has a theoretical pharmacodynamic effect of up to 24 h.¹

One of the most vexing problems in normalizing BP in RH is the provision of an adequately prescribed antihypertensive drug regimen. Inappropriate pharmacologic combinations and/or inadequate dosing are major reasons for lack of BP control. One year after identification of RH, prescription of many classes of antihypertensive medications decline.³¹ Indeed, lack of treatment intensification, not lack of medication adherence, was more closely associated with lack of BP control.³² Among the largest declines in antihypertensive medication prescription was a 12% reduction in the use of diuretics.³³ Because most patients with RH have significant extracellular fluid volume expansion, diuretics are arguably the most critical mainstay of therapy for this condition.^{1,34}

Because lack of medication adherence is so prevalent in RH, part of the medication optimization process should be careful documentation, using the most direct method possible, of medication adherence; this would best be accomplished using biochemical measurement of drugs or their metabolites in plasma or urine.

It is also important to consider the method of BP monitoring in patients with RH during the process of optimizing the triple drug regimen through drug or dose adjustment. In patients with RH, ABPM readings are associated with higher risks of CVD events and mortality than clinic BP measurements. Furthermore, on-treatment BP measurements, especially mean cumulative BP levels, are more tightly associated with these CVD outcomes than baseline BP measurements.³⁵ These findings support the use of ABPM in the on-treatment management of RH.

Step 2: Substitution of an optimally dosed thiazide-like diuretic

If one of the three antihypertensive drugs is a thiazide diuretic, or if a diuretic needs to be added to the 3 drug regimen, the next step is to substitute or add a thiazide-like diuretic (ie. chlorthalidone or indapamide). These drugs have longer half-lives than thiazides and are the diuretics of choice in RH.^{36,37} Indeed, studies have demonstrated that simply substituting a thiazide-like diuretic instead of a thiazide can result in adequate BP control in RH.^{38–40} The ability of chlorthalidone over hydrochlorothiazide to lower BP, especially nocturnal BP, is undoubtedly related to the longer half-life of chlorthalidone. Nevertheless, the use of chlorthalidone may be associated with a higher incidence of hypokalemia and/or hyponatremia compared to hydrochlorothiazide, and electrolytes should be monitored on a regular basis in patients taking chlorthalidone or indapamide.⁴¹

Because extracellular fluid volume expansion is a pathophysiologic hallmark of RH, diuretic therapy is essential for BP control. However, in the presence of CKD, the natriuretic action of the thiazides is altered. Hydrochlorothiazide does not induce predictable natriuresis at an eGFR <45 mL/min/1.73m², whereas chlorthalidone induces natriuresis at eGFR ≥30 mL/min/1.73m².⁴² Thus, for patients with mild-moderate renal disease, a thiazide-like diuretic is preferred over a thiazide diuretic.

Table 1

Once Daily, First-Line Antihypertensive Agents by Pharmacologic class used to optimize the 3-drug regimen in patients with resistant hypertension.

Pharmacologic Class	Pharmacologic Agent	Dose Range (mg/day)
Thiazide Diuretic	Hydrochlorothiazide	12.5–50
	Chlorthalidone	12.5–25
Thiazide-like Diuretic	Indapamide	1.25–2.5
	Benazapril ^a	10–40
ACE Inhibitor	Enalapril ^a	5–40
	Fosinopril	10–40
	Lisinopril	10–40
	Moexipril ^a	7.5–30
	Perindopril	4–16
	Quinipril ^a	10–80
	Ramapril ^a	2.5–20
	Trandolapril	1–4
	Azilsartan	40–80
	Candesartan	8–32
ARB	Eprosartan ^a	600–800
	Irbesartan	150–300
	Losartan ^a	50–100
	Olmesartan	20–40
	Telmisartan	20–80
	Valsartan	80–320
	Amlodipine	2.5–10
	Felodipine	2.5–10
CCB: dihydropyridine	Nifedipine LA	30–90
	Nisoldipine	17–34
	Diltiazem ^b	120–360
	Verapamil SR ^b	120–360

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LA, long acting; SR, slow release.

^a Can be administered once or twice daily.

^b Do not use in patients with heart failure with reduced ejection fraction.

Step 3: Addition of a mineralocorticoid receptor antagonist as the fourth drug

High quality evidence supports the addition of a mineralocorticoid receptor antagonist (MRA) as the fourth drug to treat RH.^{34,43–49} The pathophysiologic rationale for MRA effectiveness is based on the demonstrated extracellular fluid volume expansion and elevated circulating aldosterone, albeit not to levels encountered in overt primary aldosteronism, in these patients.³⁴ Recently, increased urinary aldosterone excretion that is non-suppressible with dietary sodium loading has been demonstrated in a large proportion of patients with RH, strengthening the rationale for MRA therapy.¹⁷

Definitive evidence for the effect of MRAs to preferentially lower BP in RH was provided by the landmark Prevention and Treatment of Hypertension with Algorithm Based Therapy-2 (PATHWAY-2) study.^{48,49} PATHWAY-2 was a double-blinded four-way crossover study that analyzed 3 months of sequential treatment with the mineralocorticoid receptor antagonist spironolactone 25–50 mg daily compared to the

β -adrenergic blocker bisoprolol 5–10 mg daily, the α -adrenergic blocker doxazosin 5–10 mg daily or placebo as add-on therapy (fourth drug) for RH. Importantly, the lead-in three drug regimen defining RH in this study consisted of a CCB, a renin-angiotensin system inhibitor (ACEI or ARB) and a thiazide-like diuretic. PATHWAY-2 demonstrated that spironolactone was superior to the two active comparators and placebo in lowering BP in uncontrolled RH. On average, spironolactone decreased home SBP by 8.7 mmHg compared with 4.5 and 4.0 mmHg with bisoprolol and doxazosin, respectively ($P < .0001$). Spironolactone controlled BP in 58% of study participants compared with 24% for placebo, 43% for bisoprolol and 41% for doxazosin ($P < .001$ for all groups). It is important to emphasize that spironolactone has not been demonstrated to be effective as a fourth drug added to any other three drug regimen than the one recommended by the 2018 AHA Scientific Statement.¹ Since participants with eGFR <45 mL/min/1.73 m² were excluded from participation, the study results do not apply to patients with CKD. Among the study participants without CKD (average eGFR 91 mL/min/1.73 m²), the occurrence of hyperkalemia was minimal.^{48,49}

Two MRAs, spironolactone and eplerenone, are available for the treatment of hypertension in the United States. Spironolactone is the more potent in terms of BP lowering, can be dosed once daily (12.5–50 mg) and is the most extensively studied in RH. However, spironolactone blocks not only mineralocorticoid receptors but also androgen receptors, leading to gynecomastia and impotence in men and menstrual abnormalities in women. While eplerenone is less effective in lowering BP, it does not block the androgen receptor and thus is not associated with reproductive hormone-like side effects. However, because of its short half-life, eplerenone (50–100 mg) must be dosed twice daily to lower BP in RH.

The use of an MRA as the fourth drug to treat RH has a major limitation in patients with CKD (eGFR <45 mL/min/1.73 m²): the occurrence of hyperkalemia. The risk of hyperkalemia increases when eGFR is <45 mL/min/1.73 m² and/or when serum potassium is >4.5 mmol/L prior to the initiation of therapy.⁵⁰ Hyperkalemia increases the risk of all-cause mortality at potassium levels ≥ 5.2 mmol/L with progressively increased risk as potassium levels rise beyond that level.⁵¹ Two possible strategies are currently being explored for patients with RH and CKD in whom MRAs are relatively or absolutely contraindicated: (1) employment of a new potassium binding agent to enable use of an MRA^{51,52}; and (2) use of a novel nonsteroidal MRA, such as finerenone, esaxerenone or KBP-5074, with a lower incidence of hyperkalemia compared to steroidal MRAs.^{53–55} These avenues may offer an opportunity to improve the use of MRAs in the future.

A sub-study of PATHWAY-2 assessed the effect of cortical collecting duct sodium channel blocker, amiloride, as an alternative to spironolactone in RH.⁴⁹ This was an open-label trial after completion of the randomized, double-blind, placebo-controlled main study protocol after which patients were crossed over from spironolactone to

amiloride. Amiloride 10–20 mg daily reduced home SBP by about 20 mmHg, an effect comparable to that of spironolactone, suggesting that amiloride can be substituted for spironolactone as the fourth drug for RH. However, the amiloride study did not have the scientific rigor of the main study; thus, additional well powered head-to-head comparative trials are required before amiloride can be recommended instead of spironolactone with confidence.

Step 4: Addition of a β -adrenergic receptor blocker as the fifth drug

Beyond the fourth drug (discussed above), there is no convincing evidence for adding or adjusting the doses of other antihypertensive agents in the treatment of RH. The following suggestions are based on practical experience and expert opinion only; one of the greatest needs in the treatment of RH is new randomized clinical trials that would inform therapeutic decision-making. If BP cannot be controlled after Step 3, consultation with or referral to a hypertension specialist may be an attractive option.

The fifth drug is often a cardioselective β -blocker (eg. metoprolol or bisoprolol) or a combined α -, β -blocker (eg. labetalol or carvedilol) if the basal heart rate is ≥ 70 beats per min. β -blockers are especially recommended in the presence of heart failure with reduced ejection fraction. Basal heart rate ≥ 80 beats per min is associated with increased risk of CVD events related to atherosclerotic CVD.⁵⁶ Although clinical trials are necessary to confirm the effect of reducing heart rate on CVD events, addition of a β -blocker holds potential to reduce events independently of BP. If β -blockade is ineffective, a centrally acting α -adrenergic agonist (eg. clonidine patch weekly or guanfacine at bedtime) can be substituted. Clonidine tablets should be avoided because multiple daily doses are usually required potentially reducing adherence and there is risk of hypertensive crisis during periods of nonadherence or withdrawal.

Step 5: Switch to a minoxidil-based regimen

Because the vasodilator hydralazine has less than optimum efficacy to lower BP and must be administered in multiple daily doses, hydralazine is not ideal as an add-on drug for RH. If BP remains uncontrolled on a combination of maximal doses of a CCB, ACEI or ARB, thiazide-like diuretic, spironolactone and a β -blocker and/or centrally acting α -agonist, an important decision is whether to switch to a minoxidil-based regimen. Minoxidil is a highly potent direct vasodilator with a wide dose range (5–100 mg/day). Minoxidil can be initiated at low dosage and titrated to higher doses (2 or 3 times a day) over several weeks. With the switch to minoxidil, other antihypertensive drugs (except β -blocker) should be tapered and discontinued. Minoxidil is associated with profound fluid retention and must be administered with a loop diuretic (eg. furosemide or bumetanide twice daily or torsemide once daily). In addition, minoxidil induces a major increase in sympathetic tone characterized by tachycardia that must be controlled using a β -blocker. Minoxidil is not well tolerated by women because it invariably induces hirsutism. However, minoxidil almost always controls BP, even in the most severe cases of RH, using a minoxidil-loop diuretic- β -blocker combination.⁵⁷

Update on renal denervation

The sympathetic nervous system plays an important role in the development and maintenance of hypertension, and renal sympathetic activity is a key component of this action. Hence, renal nerve ablation for RH has been studied for over a decade. Early studies using renal nerve ablation demonstrated promise in controlling BP in patients with RH taking 4–5 antihypertensive drugs, but these studies were uncontrolled and lacked validation by ABPM.^{58,59} The first sham-controlled randomized clinical trial, SIMPLICITY HTN-3, showed no significant effect on BP in patients with severe RH.⁶⁰ Criticisms of SIMPLICITY HTN-3 included (1) the high failure rate (75%) to achieve complete circumferential renal nerve ablation; (2) inexperienced operators; (3) increased

non-adherence to the multidrug antihypertensive regimen due to lofty patient expectations from the procedure; (4) failure to include ABPM in the efficacy analysis; and (5) inclusion of patients with isolated systolic hypertension due to vascular stiffness, which was later shown to exhibit unresponsiveness to renal nerve ablation.

Since that time, new catheters have been designed with multiple electrodes to ensure more complete renal denervation and ABPM has been applied to randomized controlled trial outcomes. The first step in that direction was The Renal Denervation for Hypertension (DENERHTN) Trial, which demonstrated a significant reduction in day-time ambulatory SBP (minus 6.7 mmHg, $P = .04$) in hypertensive patients taking 3 antihypertensive medications compared to those taking 4 antihypertensive drugs without denervation.⁶¹

A potential breakthrough for renal denervation in the treatment of selected patients with hypertension came with the recent report of the SPYRAL-OFF MED Pivotal trial.⁶² The Pivotal trial was a prospective, sham-controlled, randomized trial evaluating renal denervation independent of antihypertensive drug effects (and consequently adherence) in 331 patients at 44 sites. A multielectrode catheter allowed complete circumferential renal nerve ablation. The trial demonstrated a net 4.7 mmHg reduction in 24 h ambulatory BP and a net 6.6 mmHg BP reduction in office BP (both $P < .001$) greater than sham control values at the maximum follow up period of 3 months. The results of this trial demonstrate proof-of-principle that renal denervation effectively lowers BP at 3 months with virtually no safety issues in the absence of antihypertensive medication in hypertension. However, the reported 24 h ambulatory BP reductions were relatively small, renal sympathetic nerve activity was not assessed (norepinephrine spillover), the follow up period was too short to assess for the possibility of reinnervation and the results did not apply to RH. Thus, although the results of this study are encouraging, further studies are needed, especially in a population with RH and with longer term follow up, to gain traction as an alternative treatment for this condition.

Disclosures

Dr. Carey chaired Writing Committee for the 2018 American Heart Association Scientific Statement on Resistant Hypertension and was Vice-Chair of the 2017 American College of Cardiology/American Heart Association high blood pressure clinical practice guideline Writing Committee.

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Declaration of Competing Interest

None.

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