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MINIREVIEWS

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Achieving control of resistant hypertension: Not just the number of blood pressure medications

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Abstract

Resistant hypertension (RH) has a prevalence of around 12% and is associated with an increased risk of cardiovascular disease, progression to end-stage renal disease, and even mortality. In 2017, the American College of Cardiology and American Heart Association released updated guidelines that detail steps to ensure proper diagnosis of RH, including the exclusion of pseudoresistance. Lifestyle modifications, such as low salt diet and physical exercise, remain at the forefront of optimizing blood pressure control. Secondary causes of RH also need to be investigated, including screening for obstructive sleep apnea. Notably, the guidelines demonstrate a major change in medication management recommendations to include mineralocorticoid receptor antagonists. In addition to advances in medication optimization, there are several device-based therapies that have been showing efficacy in the treatment of RH. Renal denervation therapy has struggled to show efficacy for blood pressure control, but with a re-designed catheter device, it is once again being tested in clinical trials. Carotid baroreceptor activation therapy (BAT) *via* an implantable pulse generator has been shown to be effective in lowering blood pressure both acutely and in long-term follow up data, but there is some concern about the safety profile. Both a second-generation pulse generator and an endovascular implant are being tested in new clinical trials with hopes for improved safety profiles while maintaining therapeutic efficacy. Both renal denervation and carotid BAT need continued study before widespread clinical implementation. Central arteriovenous anastomosis has emerged as another possible therapy and is being actively explored. The ongoing pursuit of blood pressure control is a vital part of minimizing adverse patient outcomes. The future landscape appears hopeful for helping patients achieve blood pressure goals not only through the optimization of antihypertensive medications but also through device-based therapies in select

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individuals.

Key words: Resistant hypertension; Pseudoresistance; Mineralocorticoid receptor antagonists; Device-based hypertension treatment; Renal denervation; Carotid baroreceptor activation therapy; Central arteriovenous anastomosis

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Core tip: Resistant hypertension (RH) is associated with an increased risk of cardiovascular events as well as mortality. Updated American College of Cardiology and American Heart Association guidelines in 2017 promote the use of mineralocorticoid receptor antagonists, which is a major change from prior guidelines. Device-based therapies such as renal denervation and carotid baroreceptor activation have emerged as innovative treatment modalities. They are continuing to be refined to improve their safety as well as efficacy profiles. Overall more validation is needed for device-based therapies, especially in the RH population.

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INTRODUCTION

Resistant hypertension (RH) is defined as blood pressure (BP) elevation above goal despite the use of three or more anti-hypertensive medications of different classes with at least one being a diuretic, all at the maximum tolerated doses, after excluding pseudoresistance^[1].

RH is achieving more recognition as a distinct category of hypertension. It has its own pathophysiology, patient characteristics, and consequences. This subgroup of patients carries higher risk for cardiovascular morbidity and mortality and may benefit from special diagnostic and therapeutic approaches to control their BP. Therefore, RH needs its own set of solutions, which may eventually include treatment modalities outside of lifestyle modification and medication-based therapies.

Following an accumulation of results from more recent clinical trials, major medical organizations across the globe have published specific RH guidelines with updated recommendations on proper diagnosis and multi-step treatment algorithms. The American College of Cardiology (ACC) and American Heart Association (AHA) were two societies to release joint updated guidelines in 2017^[2]. AHA has also released an updated scientific statement that comprehensively reviews the current body of evidence pertaining to RH^[1]. In 2018, the European Society of Cardiology/European Society of Hypertension (ESC/ESH) published updated guidelines for management of arterial hypertension, and included a section specifically for RH^[3].

The pathogenesis of RH is not fully understood, but is thought to be a combination of fluid retention, sympathetic system activation, and arterial stiffness^[4]. Aldosterone has emerged as a key player in these mechanisms, making mineralocorticoid receptor antagonists (MRA) that much more important in the treatment for RH^[4].

Population-based studies estimate the prevalence of RH to be 10%-15%^[1]. The negative health impact on the lives of this group of patients is far-reaching. Patients with RH have an increased risk of cardiovascular disease such as non-fatal myocardial infarction, congestive heart failure, coronary heart disease, and stroke^[5-8]. In addition, these patients also are at risk of developing chronic kidney disease and end-stage renal disease, as well as increased all-cause mortality^[7-11].

In addition to lifestyle modifications, medication-based treatment has been the mainstay of BP control since the 1930s, and continues to be the only widespread method currently used to treat RH. Standard treatment regimens consist of selecting not only from a variety of drug classes, but also mechanistically complementary ones. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers, diuretics, and beta-blockers continue to be the commonly used pharmacologic agents. The validation of MRAs in the treatment of

RH from recent randomized clinical trials has led to adoption of evidence-based standards for their use^[2].

Although medications are the basis of hypertension management, even as early as 1938 there was experimentation with a non-medication approach for BP reduction with the thoracolumbar sympathetic chain removal^[12-14]. Despite the disastrous consequences of that particular modality, the concept of a non-medication approach endured. Today there are several device-based treatments being actively studied in clinical trials, including renal denervation (RDN), carotid baroreceptor activation therapy (BAT), and central arteriovenous (cAV) anastomosis.

DIAGNOSIS OF RH

As previously stated, the definition of RH is BP elevation above goal despite the use of three or more anti-hypertensive medications of different classes, with at least one being a diuretic, all at the maximum tolerated doses after excluding pseudoresistance^[1-3]. If BP is controlled with the use of four or more anti-hypertensive medications, this is called *controlled* RH^[1]. A key part of this definition is that pseudoresistance must be ruled out first.

Pseudoresistance

Pseudoresistance has four common etiologies including inappropriate measurement, sub-optimal prescribing (clinician inertia), white coat hypertension, and medication nonadherence. Medication nonadherence makes a sizeable contribution to pseudoresistance. One large meta-analysis concluded that between 31%-50% of those labeled as having RH are simply nonadherent to their medication regimens^[15]. In all of the major clinical trials involving BP monitoring, ensuring adherence is always a notable concern. Otherwise, adherence can strongly influence the results. This was pointedly displayed in the SYMPLICITY-HTN 3 trial, where a post hoc analysis concluded that variable patterns of medication adherence played a significant part in producing results that were different from prior trials in the series, SYMPLICITY HTN 1 and 2^[16,17]. Adherence to medication can be measured both indirectly through self-reported questionnaires (SRQs), and also *via* direct means. The imperfect gold standard currently used is the Medication Event Monitoring System (MEMS), where a sensor is placed in the medication vial cap to record every time the bottle is opened^[18]. Trials have used a variety of methods to assess adherence, such as liquid chromatography and mass spectroscopy, patient self-reporting or pill count^[17]. The inherent difficulty of properly measuring adherence is obvious, but not easily solved. The cost of implementing such direct measures is a significant barrier. As pharmacology literature suggests that there is at least moderate correlation between SRQs and MEMS, patient self-reporting will likely continue to be in widespread use^[18].

A second major contributing factor to pseudoresistance is white coat hypertension, which is defined as in-office BP measurements above the threshold to be considered as hypertensive with out-of-office BP readings being lower and within goal range. The prevalence of white coat hypertension ranges from 15%-40% in the outpatient setting and should be ruled out in all cases of in-office hypertension^[19]. Both ACC/AHA and ESC/ESH guidelines conclude that it is reasonable to screen for the presence of white coat hypertension using either ambulatory BP monitoring or home BP monitoring prior to the diagnosis of hypertension^[2,3].

Similarly, inappropriate measurement of BP in the clinic setting should also be considered in cases of labeled RH. Bhatt *et al*^[20] reported that in 130 patients noted to have uncontrolled hypertension by triage vitals, 33% of them were actually mislabeled and had controlled BP when checked with an automated BP machine during the same visit after sitting quietly in a room for 5 min. According to both European and United States major guidelines, patients should be seated with their backs supported and feet on the floor for at least 5 min, the cuff properly selected based on arm circumference, and arm supported at the level of the heart^[2,3,21-25]. Although the gold standard is the use of mercury sphygmomanometer, many automated BP cuffs have been validated and are acceptable for use in clinical practice^[21]. Whether using the manual or automated approach, the principles listed above still apply.

Although nonadherence, inappropriate measurement, and white coat hypertension are all major components of pseudoresistance, unfortunately there is also a contribution from the side of the healthcare providers. Clinician inertia is described as failure by the provider to intensify treatment as indicated^[24]. An oft-cited but apropos study of 800 male patients receiving care at five outpatient Department of Veterans

Affairs centers revealed that despite 40% of the patients having elevated BP readings at their clinic visits, only at 6.7% of the visits were the BP regimens intensified as indicated^[25]. Another analysis from a large ambulatory care survey with over 19000 patients showed that providers were not prescribing anti-hypertensives according to the current ACC/AHA guidelines, even though they had been published two years earlier^[26]. Some of the reasons behind clinician inertia include over-estimation of the care being given already, unsupported decision making that ends up delaying care, as well as lack of knowledge of how to achieve BP goals^[24,27,28].

Appropriate investigation for secondary causes of hypertension

All cases of RH should be explored for secondary causes of hypertension as listed in [Table 1](#)^[1,29,30]. Parts of the history may lead the provider to strongly consider one cause over another, but the appropriate lab and imaging workup should be done in all patients with confirmed RH. Of note, one of the most common causes of RH is obstructive sleep apnea (OSA), with estimates ranging from 60%-80%, making this an important patient population to identify early^[31,32].

Excluding interfering substances

As summarized in [Table 2](#), there are many medications ranging from chemotherapy all the way to common over-the-counter remedies, herbal supplements, food items, and illicit substances that are known to raise BP^[29,33,34]. Therefore any of these substances should be considered during the initial evaluation of a patient.

Diagnostic approach to RH is summarized in [Figure 1](#).

PREVALENCE

Our best estimate of the prevalence of RH based on the range of data accumulated is between seven and eighteen percent. The true prevalence is uncertain and varies depending on study populations and study settings. This is in part due to how past studies defined RH by BP readings and medication lists without being able to assess medication adherence and optimization. Undoubtedly, this ambiguity results in a percentage of patients being labeled as treatment resistant when in fact they are only nonadherent, or the doses of their medications are suboptimal. Apparent treatment RH is a new term that has been created recently to better characterize this known issue among studies defining the prevalence of RH. It is used when data on patient adherence, medication dose, or out of office BP data is missing, causing an inability to exclude pseudo-resistance^[1].

The proportion of patients with RH among treated hypertensive patients is reported to be around 10%-15% in population based studies, and slightly higher at 15%-18% in clinic-based studies^[1]. Roughly 9% of hypertensive adults in the United States met criteria for RH in the National Health and Nutrition Examination Survey (NHANES) from 2003 through 2008^[35,36]. This represented 12.8% of patients on antihypertensive drug therapy^[36]. For any population data analysis, the influence of pseudo-resistance on the data cannot be ignored. For example, in a cohort of 68045 patients in Spain, the prevalence of RH dropped from 12.2% to 7.6% after excluding white coat hypertension, one of the factors in pseudo-resistance^[37]. In addition, a recent meta-analysis of 91 worldwide population-based studies including 3.2 million patients on treatment for hypertension found the prevalence of true-RH to be 10.3% after excluding pseudo-resistance^[38].

PATHOGENESIS

The pathogenesis of RH is not fully understood, but is thought to be a combination of several mechanisms. Part of the difficulty of elucidating pathogenesis is the overlap between RH and other well-defined pathological states, such as obesity and chronic kidney disease (CKD), so that it is unclear if the mechanisms are unique to RH or merely stemming from the other concomitant conditions. The three most significant underlying processes that have been linked to RH are fluid retention, sympathetic system activation, and arterial stiffness^[4]. Excess fluid retention can be caused by excess salt ingestion, impaired renal natriuresis, as well as increased aldosterone production^[4]. Aldosterone is of particular interest in RH not only because it induces salt retention and thereby fluid retention, but also because of other non-genomic pro-inflammatory effects that can promote a pharmacologically resistant state^[39,40]. Thus, mineralocorticoid receptor blockade becomes much more important in RH, a fact that has been reflected in the 2017 ACC/AHA guidelines and the 2018 AHA scientific

Table 1 Causes of secondary hypertension and initial screening tests¹

Hyperaldosteronism	Serum renin-aldosterone ratio
Renal parenchymal disease	Serum creatinine
Obstructive sleep apnea	Polysomnography
Pheochromocytoma	Serum metanephrine and 24-h urine catecholamines
Renal artery stenosis	Renal artery duplex
Coarctation of the aorta	CT angiogram
Cushing's disease	24-h free urinary cortisol and late-night salivary cortisol ¹
Thyroid disease	TSH and freeT4
Acromegaly	Serum growth hormone

¹Adapted from Carey *et al*^[1], Charles *et al*^[29], and Rimoldi *et al*^[30].

statement, which now include MRAs as one of the front-runner drug classes for RH^[1,2]. In addition to fluid and salt retention, sympathetic system activation is a cornerstone mechanism for RH^[12]. Using norepinephrine regional spillover techniques, researchers have found statistically significant activation of renal sympathetic system in patients with RH when compared to both healthy subjects and those with non-RH^[41]. Lastly, arterial stiffness is thought to be another major mechanism. There are numerous underlying processes in the pathogenesis of arterial stiffness, some of which include endothelial dysfunction, salt consumption, and sympathetic signaling^[42]. Several studies have shown that RH patients have higher arterial stiffness than those with controlled hypertension^[43-45]. Increasing arterial stiffness leads to increasing BP, which in turn increases arterial stiffness, and on and on the vicious cycle goes^[44,45].

GUIDELINE UPDATES

Before pharmacologic or other intervention for RH can commence, it is recommended to exclude secondary forms of hypertension and white coat hypertension. Guidelines from the ACC/AHA have been consistent on these evaluations for some time, though recently more emphasis has been placed on ambulatory BP monitoring to exclude white coat hypertension and detect masked hypertension.

According to the 2018 AHA Scientific Statement on the detection, evaluation, and management of RH, as well as ESC/ESH guidelines, patients should be on maximally tolerated doses of mechanistically complementary antihypertensive agents^[1,3]. This would normally include an ACEi or ARB, a long acting calcium channel blocker, and a diuretic that is appropriate for the patient's underlying kidney function^[1,3]. One consideration to make before adding another medication to the patient's therapeutic regimen would be whether the patient would benefit from switching from hydrochlorothiazide to either chlorthalidone or indapamide. Chlorthalidone or indapamide produce a more predictable natriuresis than hydrochlorothiazide below an eGFR of 45 mL/min/1.73 m²^[1]. This produces a greater reduction in plasma volume which is of importance in RH linked to fluid overload. Switching from hydrochlorothiazide to the same daily dose of chlorthalidone has been shown to produce reductions in BP of 7-8 mmHg in studies comparing the two medications^[46,47].

Recent changes to the treatment algorithm for RH now include emphasis on MRA. This new addition to the evidence-based algorithm for RH is based on multiple randomized controlled trials published over the last 10 years^[47-50]. The addition of a MRA to a patient's BP regimen is now recommended if his or her BP remains above goal despite maximally tolerated doses of three antihypertensive agents including a diuretic appropriately administered for the patient's renal function. MRAs can be more effective than the addition of alpha- or beta-blockers in patients with low renin status or salt sensitivity^[51]. The once daily administration of spironolactone, combined with its effectiveness at doses as low as 12.5 to 25 mg, make it an ideal fourth agent in most patients. Ideal patients for initiation of spironolactone have an eGFR > 45 mL/min · 1.73 m² and a baseline serum potassium of < 4.5 mmol/L due to the increased risk of hyperkalemia. Adverse effects at higher doses include gynecomastia and erectile dysfunction in men, and irregular menses in women.

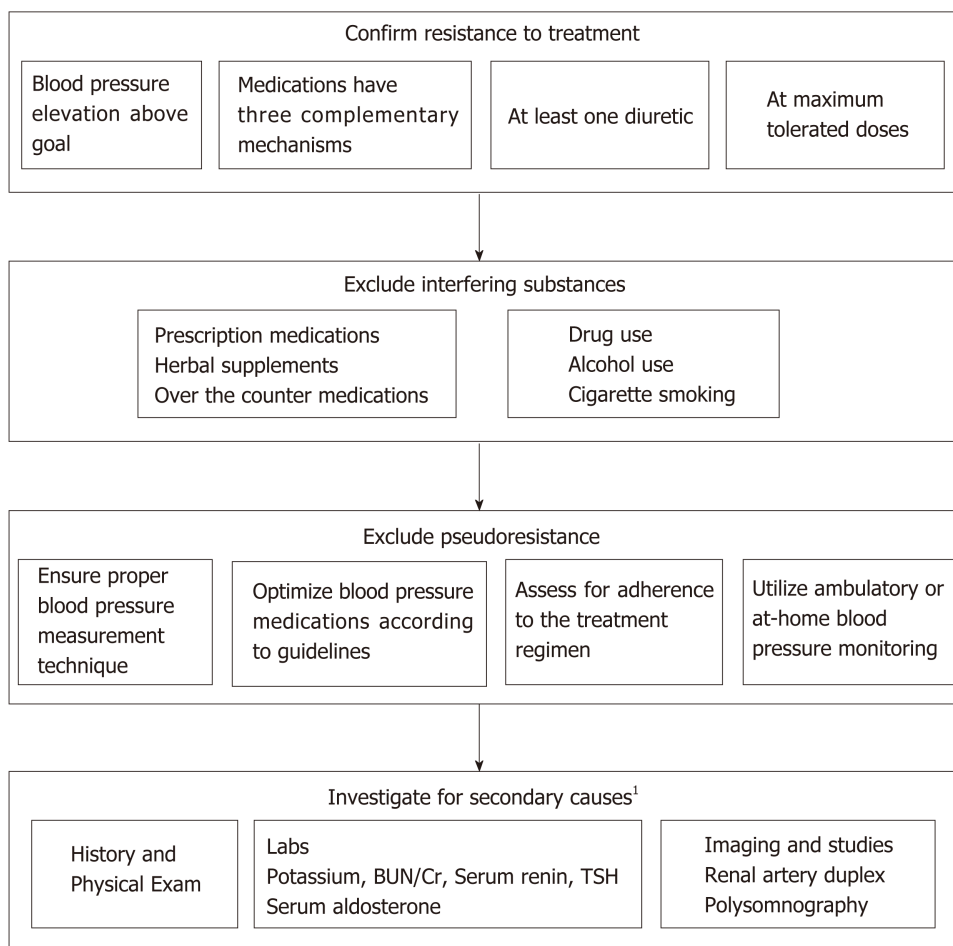


Figure 1 Diagnostic approach to resistant hypertension.¹Only some of the diagnostic tests are listed here, as the history and physical will direct more specific and detailed workup.

LIFESTYLE FOCUS

Dietary sodium

Since the 1980s, it has been recognized that reducing dietary sodium intake can modestly reduce systolic blood pressure (SBP) 2-10 mmHg and diastolic blood pressure (DBP) 1-6 mmHg, and can improve the likelihood of successfully withdrawing anti-hypertensive medications^[52-56]. It was during this era that the now ubiquitous Dietary Approaches to Stop Hypertension (DASH) diet, which limits salt intake to less than 2300 mg daily among other dietary restrictions, was shown to be effective not only for weight loss but also for BP reduction^[52]. Multiple analyses since that time continue to show that lower salt intake can help in reducing BP^[57,58]. All major guidelines for management of essential hypertension include a low salt diet, with recommended consumption limited to less than 2300 mg per day^[2,3,59].

The RH population has also been studied in regard to low salt diet, and they had dramatic reductions of BP, on average 22.7/9.1 mmHg, which is much more than in patients with essential hypertension^[60]. Since there is over-whelming evidence for BP reduction in the rest of the hypertensive population including CKD patients, it is recommended that patients with RH subscribe to a low salt diet of less than 2300 mg per day. However, there are more studies needed to identify the ideal level of salt restriction in the RH population.

Obesity

The worldwide epidemic of obesity has been well described, with the prevalence of obesity tripling between 1975 and 2016^[61]. According to the NCD Risk Factor Collaboration data, between 1975 and 2014, the obesity prevalence in men increased from 3.2% to 10.8, and in women 6.4% to 14.9%^[62]. The highest rate of obesity in the world is within the United States with most recent CDC data reporting a prevalence of 39.8% of the adult population^[63]. Various studies have shown that obesity correlates with having hypertension. The NHANES population data supports this, reporting

Table 2 Medication and drugs known to cause hypertension^[29,33,34]

NSAIDs
Estrogens/Progestins
Anabolic Steroids
Corticosteroids
COX-2 Inhibitors
SSRI/SNRI
Tricyclic antidepressants
Lithium
Buspirone
Carbamazepine
Calcineurin inhibitors
Pseudoephedrine
Amphetamine derivatives
¹ Chemotherapy agents
Caffeine
Methamphetamines
Cocaine
Ginseng, St John's Wort, Ephedra, Yohimbine
Alcohol

¹Paclitaxel, alkylating agents, sorafenib, vascular endothelial growth factor inhibitors, *etc.* NSAIDs: Non-steroidal antiinflammatory drugs.

that 36% of obese patients also have hypertension^[64-66]. New evidence is emerging that obesity also increases the risk of RH. The underlying mechanism is multifaceted and involves signaling from adipokines, the renin-angiotensin-aldosterone pathway, and adipose-induced endothelial dysfunction^[67]. There is a high level of evidence, including evidence from many randomized controlled trials, that even a 5 kg weight loss can lead to a reduction in BP in a population without RH^[52,68-70]. A 5%-10% reduction of body weight continues to be a front-line recommendation in both older and newer hypertension management guidelines in both the United States and Europe^[2,3]. However, it is worth noting that weight loss in patients with RH is understudied to date^[1]. In addition, the long-term BP lowering effects appear to be somewhat attenuated, with the biggest gains happening in the initial stages of weight loss followed by a reduction in gains^[71]. It is also possible that the long term effects are simply not being observed by the current studies due to limited duration of follow up^[71,72]. Although weight loss has tremendous health benefits, it is very difficult for patients to sustain a lower weight over time^[67,73]. Considering this, along with the lack of data in RH patients, weight loss may have limited potential as a long-term tool for BP reduction in this group.

Exercise

Physical exercise has been extensively studied and has consistently been shown to reduce both SBP and DBP^[74]. There are different forms of exercise including aerobic activity, isometric exercises, resistance training, and a combination of any of the above, and each category has been studied for BP lowering effect. Based on results from a large meta-analysis, aerobic activity had a mean BP reduction of 10.8/4.7 mmHg, which was the largest reduction of BP of all the exercise types^[75]. Isometric exercises also show significant BP reduction^[74,76-78]. Dynamic resistance seems to have a modest but significant BP lowering effect in hypertensive individuals when compared to normotensive individuals, with slightly greater effect when using larger muscle groups^[78-80]. Exercise has been recommended in major guidelines for hypertension for many years, and continues to be a core lifestyle modification in both the recent ACC/AHA guidelines for RH as well as ESC/ESH guidelines for hypertension^[2,3]. Although the RH population has not been studied extensively in this regard, there have been a few small trials that have already shown BP reduction with moderate level activity^[81,82].

MEDICATION-BASED THERAPIES

Pharmacologic therapy for the treatment of RH includes combinations of three or more drugs of different classes, including a diuretic^[1]. The choice of agents should be tailored to the individual patient. Factors to consider include prior effect of medication, history of adverse events, intolerances, allergies, financial limitations, and the presence of diabetes, chronic kidney disease, and other comorbidities. NHANES data between 2005 and 2008 showed that in patients with uncontrolled BP on at least 3 medications, the most commonly used classes of medications other than diuretics were ACEi (50.8%), ARB (39.1%), beta-blockers (62.1%), dihydropyridine calcium channel blockers (40.0%), and non-dihydropyridine calcium channel blockers (18.9%)^[83].

MRA

Over the last 10 years, observational studies and randomized controlled trials have accumulated evidence supporting MRAs, including eplerenone and spironolactone^[48,49]. In 2011, the ASPIRANT trial included 111 patients who were all on diuretics, with a majority on a beta-blocker, calcium channel blocker, and either an ACEi or ARB^[84]. In this study, patients randomized to 25 mg of spironolactone saw a significant reduction in SBP in the office (8.6 mmHg) and ambulatory setting (6.5 mmHg)^[84].

A Denmark-based, multicenter, double blind, randomized, placebo-controlled study in 2013 added 25 mg of Spironolactone to 119 patients who were on triple therapy for RH^[49]. Average daytime placebo-corrected SBP was reduced by 8.9 mmHg. Also, office, night-time and 24 h BP as well as pulse pressures were reduced significantly^[49]. Urinary albumin to creatinine ratio was also significantly reduced in the spironolactone group.

A comparison between Spironolactone, Doxazosin, Bisoprolol, and a placebo was the focus of the PATHWAY-2 trial conducted at 12 different centers in the United Kingdom^[48]. The mean reduction of baseline BP observed in the Spironolactone group was 14.4 mmHg. This was found to be statistically significant when compared to placebo, Doxazosin, or Bisoprolol, which reduced BP by 4.2 mmHg, 9.1 mmHg, and 8.4 mmHg respectively. No statistically significant difference was observed between agents with regards to serious adverse events or patient withdrawals due to adverse events.

A meta-analysis that included the three aforementioned randomized controlled trials in addition to a Brazilian open-label, parallel randomized trial (ReHOT), showed that adding on Spironolactone to the treatment regimen of patients with RH had a mean reduction of SBP and DBP of 16.67 mmHg and 6.11 mmHg, respectively^[51,85]. It is important to note that the rates of serious adverse effects, including hyperkalemia, or patient withdrawals from the trials tended to be higher in patients treated with spironolactone than placebo^[85]. This meta-analysis, in conjunction with these randomized controlled trials, has influenced the evidence-based treatment algorithm now published by the ACC/AHA in their latest guidelines.

Individualized therapy

Expert opinion also offers specific methods to guide treatment. The pharmacologic management of RH is summarized in the AHA 2018 scientific statement and is based on the currently available clinical evidence^[1].

Briefly, if, after the addition of a MRA to the patient's existing 3 BP medication regimen, the patient's BP remains uncontrolled, this should trigger an assessment of the patient's resting sympathetic tone and its contribution to the patient's RH. A simple way to complete this assessment is to assess the patient's resting heart rate. If his or her heart rate is above 70 beats per minute, an addition of a beta-blocker is a reasonable addition. If there exists a contraindication to beta-blockade, a central acting alpha-2 agonist, such as clonidine, can be considered. The patch form of clonidine has less risk of rebound hypertension after discontinuation or nonadherence.

If BP is not controlled after addition of either beta-blockade or clonidine, hydralazine is an additional option. Doses less than 150 mg per day decrease the chance of developing drug-induced lupus. The addition of nitrates to hydralazine in cases of heart failure is generally recommended.

Minoxidil should be withheld until all other options are exhausted due to its high rate of discontinuation from frequent dosing and adverse effects, including hirsutism. In addition, minoxidil must be given with both a loop diuretic and a beta-blocker due to a predictable increase in sympathetic tone and sodium retention. It is generally recommended that such individualized therapy must occur with close follow up for medication titration and monitoring for adverse effects.

DEVICE-BASED TREATMENT

Evidence from numerous animal studies and physiological studies demonstrate that sympathetic activation is a key mechanism for not only essential hypertension, but also RH^[12,41,86,87]. Most device-based therapies attempt to control BP by interfering with sympathetic signaling and thereby disrupting this crucial mechanism of hypertension.

Renal denervation therapy

The renal sympathetic supply has been a promising target given the physiological link between sympathetic input and hypertension^[41]. Renal denervation therapy (RDN) is a device-based therapy to ablate the renal sympathetic nerves by radiofrequency or ultrasound waves emitted by an endovascular catheter. RDN showed early promise after both its human feasibility trial (SYMPPLICITY HTN-1), and a larger randomized prospective study (SYMPPLICITY HTN-2), demonstrated not only a reduction of in-office BP, but also an acceptable safety profile for the device^[88,89]. The subsequent trial, SYMPPLICITY HTN-3, halted the enthusiasm. SYMPPLICITY HTN-3 was a single blind, randomized, sham-controlled trial, arguably the most robust design out of the studies. The results were surprising and also sobering to the field of RDN with no significant difference in in-office BP measurements between the sham procedure group and the RDN group^[90]. Extensive analysis has been done to explain the contradictory findings. Prominent explanations include incomplete nerve ablation due to poorly designed catheter electrodes, proceduralists' unfamiliarity with the technique, and variable BP medication adherence in the study participants^[41,91,92].

Since SYMPPLICITY HTN-3, the catheter ablation device has been re-designed to allow for circumferential and thus more complete ablation (Symplicity Spyral™ Multi-electrode Renal Denervation Catheter, MedTronic). With the newly designed device and specially trained proceduralists, new trials have already started. SPYRAL HTN-OFF MED is a proof of concept trial. Early results have shown significant blood pressure reduction; however, this study population of hypertensive patients are treatment naïve and therefore do not have RH by definition^[93]. Similarly, the SPYRAL HTN-ON MED trial, which has selected a hypertensive population being treated with one to three BP medications, has shown significant reduction of BP in the RDN group compared to the sham-control^[16].

RDN can also be accomplished *via* ultrasound (Paradise Renal Denervation System, ReCor Medical) instead of radiofrequency. This technique has also shown successful reduction of BP in its own proof of concept trial, RADIANCE HTN SOLO^[94].

The results of SYMPPLICITY HTN-3 have prompted persistent strides in the field of RDN to improve the technology and study designs, and to continue researching this methodology as a means of BP control. Although some of the preliminary results are promising, there is still more testing that is needed. As RH patients have the most to gain from such therapies, it will be imperative that future studies include this population.

Carotid BAT

The carotid baroreceptor reflex is triggered by wall stretch or a rapid rise of pressure within the carotid body leading to decreased sympathetic signaling to the vasculature, heart, and kidneys, with a combined effect of lowering systemic blood pressure^[95,96]. Today there are human clinical trials underway to assess BAT as a means of hypertension treatment^[97].

Two BAT devices are being actively studied in humans, an implantable pulse generator (Rheos™ and BAROSTIM NEO™) by CVRx, and an endovascular device MobiusHD™ by Vascular Dynamics. In the Rheos™ system, an implantable pulse generator is surgically inserted into the subcutaneous tissue of the infraclavicular region, and bilateral electrode leads are then connected to the outside of the carotid body and tunneled subcutaneously^[96,97]. The generator sends electrical impulses to the carotid sinus and activates the baroreceptor mechanism^[96]. After two feasibility studies, The Rheos Feasibility Trial and the DEBuT-HT study^[97,98], the Rheos Pivotal Trial was started with a sham control design in which the control group had the device implanted but not activated until 6 mo into the study. Although it failed to show a superiority of BAT to reduce BP compared to medical therapy after 6 mo (its short term efficacy end point), more than 50% of those with BAT were able to achieve a SBP < 140 mmHg^[99]. In 2017, a 6-year follow up report of patients from all three aforementioned trials was released. The results showed a sustained reduction in both SBP and DBP^[100].

There have been safety concerns related to the activation of the baroreceptor reflex, such as hypotension and bradycardia, but these effects were short in duration^[97-100]. In addition, there are concerns related to the procedure itself, including cranial nerve injury, which occurred in 9.2% of The Rheos Pivotal Trial, albeit only 4.8% of patients

had residual effects^[99]. This event rate is similar to the range of 4%-12% reported in the cardiovascular surgery literature for patients undergoing carotid endarterectomies^[101-103]. The investigators of the Rheos Pivotal Trial did note that about 76% of the patients with procedure-related events did not have long lasting sequelae.

The concern about the safety profile is being answered in several ways. Firstly, CVRx has designed a second generation pulse generator that has only a unilateral electrode, and requires a smaller procedure for insertion^[104]. This has already completed a feasibility study, and is on schedule for a randomized, double blind, parallel study for further study (The Nordic BAT)^[105,106]. A second answer to the safety concerns is the MobiusHD™ endovascular device by Vascular Dynamics. This device is a self-expanding nitinol implant that is deployed endovascularly^[106]. Two large, open label, multicenter trials, CALM-FIM-EUR and CALM-FIM-US, recently published data which demonstrated safety of this approach as well as efficacy in lowering BP^[106,107]. Currently, a randomized, double blind, sham controlled pivotal trial, CALM-2, is underway^[108].

CAV anastomosis

In addition to the well-studied RDN and BAT, there is also a surgical procedure utilizing the ROX Coupler (by ROX Medical) device, in which a small stent is placed through an endovascularly created anastomosis between the femoral artery and vein. This self-expanding stent is left in place, and will divert arterial blood flow in to the venous system. The Rox Coupler has been investigated in an open label randomized trial, and has shown efficacy in lowering BP^[109]. There is ongoing study of this device, and the results and safety profile will be something to follow in the years ahead. Therapeutic targets in RH are summarized in [Figure 2](#).

LOOKING FORWARD

Medication-based therapies

The progression of medication therapy for RH in the last 10 years is based on increasing evidence for current antihypertensive medications. The use of clonidine, minoxidil, and hydralazine for RH is now currently supported by expert opinion. In the future, we would expect the addition of one or more of these agents to the evidence-based algorithms supported by professional organizations once new trials have been conducted to establish their efficacy beyond currently recommended medical therapy.

Device-based therapies

The ongoing efforts of device and procedural refinement make both RDN and BAT potential options for BP control in the future. Over the next few years there will be more data coming out of RDN clinical trials, including the use of an ultrasound emission as opposed to radiofrequency. Although the early trial (SPYRAL HTN OFF MED) with the newly designed catheter assembly was conducted in patients without RH, the BP lowering effects are still notable, and likely there will be an expanded study to include patients with RH. BAT remains promising, with six-year follow-up data confirming ongoing BP control and device safety profile. This device-based therapy will be at the forefront of research in the years to come. cAV anastomosis is a unique approach and may be of particular benefit to those with increased arterial stiffness as a cause of RH, but the long-term safety of this approach is a major question that needs to be answered.

CONCLUSION

Patients with RH comprise a notable and formidable subset of the hypertensive population, who have increased cardiovascular risk and mortality. Providers must be able to promptly identify these patients, accurately assess the degree of treatment resistance by excluding pseudoresistance, then not only intensify but also optimize medication regimens to align with updated guidelines, including the routine use of MRA as indicated. Device based therapies such as renal denervation and BAT are on the horizon but need continued study, especially in the RH population.

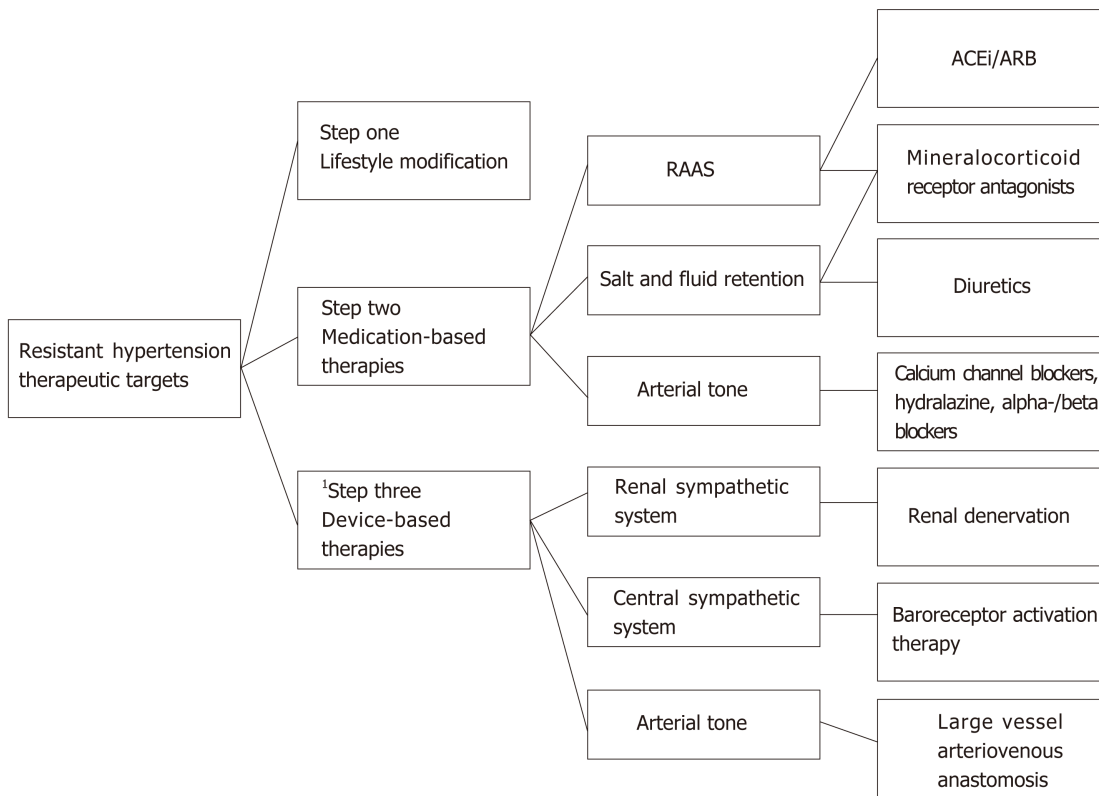


Figure 2 Therapeutic targets in resistant hypertension.¹Step one and step two are part of guidelines and apply to all patients. Step Three involving device-based modalities is still being studied, and is not yet recommended or in widespread clinical use. RAAS: Renin Angiotensin Aldosterone System; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.

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