



# Review Article

## Resistant Hypertension 2018

Abraham Oomman<sup>1</sup>, K. Abhinaya<sup>1</sup>

<sup>1</sup>Department of Cardiology, Apollo Hospitals, Chennai, Tamil Nadu, India

### Abstract

Resistant hypertension (HT) (RH) is defined as blood pressure (BP) that remains elevated above the target despite simultaneous treatment with three antihypertensive agents of different classes, at maximum or maximally tolerated doses and at the appropriate dosing frequency. Patients requiring four or more antihypertensives to achieve BP targets are also included. About 12–15% of individuals treated for high BP would have RH. They are at higher risk of cardiovascular morbidity and mortality. White coat effect and pseudohypertension should be ruled out before diagnosing RH. Drug compliance and assessment for comorbidities such as sleep disturbances, obesity, diabetes, and secondary HT are important. The treatment is primarily lifestyle and risk factor modification as well as pharmacotherapy. Diuretics, especially spironolactone and eplerenone, should be used appropriately. Divided dosing, bedtime dosing, and use of fixed-dose combinations should be applied. Renal artery stenting for significant renal artery stenosis is useful in carefully selected subsets. Among interventional approaches, renal denervation (RDN) showed initial promise, but sham-controlled trial could not prove a significant benefit. Modifications of the RDN techniques hold promise. Other interventional techniques such as baroreceptor activation therapy still need further studies. In addition, clinical inertia by the physician should be avoided.

**Key words:** Resistant hypertension, hypertension, secondary hypertension, renal artery stenting, renal denervation, target blood pressure

### Introduction

Non-communicable diseases are becoming the leading cause of morbidity and mortality worldwide. Hypertension (HT) is a major cause of cardiovascular disease, especially stroke, myocardial infarction, and renal failure. The incidence of HT *per se* is increasing and stricter and lower definitions of HT is also contributing to it. Resistant HT (RH) is a challenging subgroup with a worse prognosis.

### Terminologies

Varied terminologies have been used in relation to RH. Controlled, uncontrolled, apparent, true, easy to treat, and difficult to treat are some of the different terminologies used in relation to RH. Uncontrolled HT is not synonymous with RH. It includes subjects who do not achieve blood pressure (BP)

targets on treatment. This includes those with poor adherence and undetected secondary HT, those on insufficient treatment protocols, and those with true treatment resistance. RH forms only a small but very significant proportion of uncontrolled HT.

### Definitions

BP that remains above the goal despite compliance with full doses of three or more antihypertensive drugs of different classes (one of the three being a diuretic) with the treatment plan also including adequate lifestyle modifications can be considered as RH. This includes patients who achieve targets with four or more antihypertensive agents.

The AHA scientific statement 2018 defines RH as “above-goal elevated BP in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin

### Address for correspondence:

Dr. Abraham Oomman, Department of Cardiology, Apollo Hospitals, Greams Road, Chennai, Tamil Nadu, India.  
E-mail: abrahamoomman@gmail.com

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system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. RH also includes patients whose BP achieves target values on  $\geq 4$  antihypertensive medications. The diagnosis of RH requires assurance of antihypertensive medication adherence and exclusion of the “white-coat effect (WCE)” (office BP above goal but out-of-office BP at or below target).<sup>[1]</sup>

The 2018 ESC/ESH Guidelines for the management of arterial HT definition of RH is similar to the AHA scientific statement 2018 except that the treatment goal was set as  $<140/90$  mmHg instead of  $<130/80$  mmHg as per the ACC/AHA guidelines.

Apparent Treatment RH (aTRH) is a term used when either medication dose, adherence or out-of-office BP is missing, thereby making pseudo resistance non-excludable.<sup>[2]</sup> BP should be measured using correct methodology before labeling as RH. Ambulatory BP measurements (ABPM) or home BP monitoring (HBPM) allows WCE to be ruled out. Patients with WCE have a prognosis similar to that of controlled hypertensives. Suboptimal adherence is seen in a large majority (50–80%) of HT patients on antihypertensive medications.<sup>[3]</sup> ABPM, correct technique for BP measurement and confirming drug compliance, helps to rule out pseudo resistance. Marked arterial stiffening may be seen in the elderly, especially those with heavy calcification of arteries. This can prevent occlusion of the brachial artery, resulting in pseudo-HT.

### Prevalence

The prevalence of aTRH in hypertensive adults on treatment varies in the population from 12% to 15% in population-based studies and 15–18% in clinic-based studies.<sup>[1]</sup> In the Spanish data, RH was 12.2% of the total treated population, of which 7.6% were true RH and 4.6% WCE.<sup>[4]</sup>

### Pathophysiology

The exact mechanism of resistant HT is unknown, but it is most likely multifactorial with the interplay of an enhanced sympathetic tone and fluid retention. Aldosterone likely has an important role in RH. Hyper-enhanced adrenergic state is present along with impaired baroreflex activity.

### Prognosis of RH

Combined outcomes of death, myocardial infarction, heart failure, stroke, or chronic kidney disease (CKD) over a follow-up of a median of 3.8 years in a retrospective study of  $>200,000$  patients with incident HT were 47% more likely in RH.<sup>[5]</sup> The effect of BP control on hypertensive patients with RH and without RH is different. A 13% reduction of risk of incident stroke, coronary heart disease, or heart failure was seen in RH compared with a 31% lower risk in those without RH.<sup>[6]</sup> It is

possible that the benefit of BP lowering may be less in patients with RH compared with hypertensive non-RH patients.<sup>[1]</sup>

### Patient Characteristics

Obesity, diabetes mellitus, undiagnosed DM, metabolic syndrome, advancing age, albuminuria, CKD, left ventricular hypertrophy, higher Framingham 10-year risk score, obstructive sleep apnea, excess salt intake, depression, and African American ancestry have been associated with RH. Up to 60–84% of RH patients have sleep apnea. Sleep deprivation including shorter sleep duration, reduced sleep efficiency, and less rapid eye movement sleep has been reported to be associated with RH.<sup>[7]</sup> A genetic link to RH has also been postulated. However, only candidate gene studies have been performed for RH and included only small samples.<sup>[8]</sup>

### Diagnosing RH

#### Identifying and correcting non-adherence to medication

Adherence to and persistence of therapy and lifestyle modifications are of utmost importance in the management of RH. Pill counts, self-report medication adherence assessment tools, pharmacy databases, pharmacodynamic parameters (heart rate and B-blockers), witnessed intake of medication, event monitoring systems, urine and blood metabolite assessment, urine fluorometry, and electronic pillboxes have been tried with varying success. Useful techniques include a patient-centric approach to reduce pill burden, using low-cost and generic drugs and fixed dose combinations. Effective strategies include improving adherence by once-daily dosage of antihypertensives when possible instead of multiple daily doses as also using fixed-dose combination agents. White coat effect and poor BP measurement techniques need to be identified and addressed.

#### Clinical inertia

This is the failure of health-care providers to initiate or intensify therapy when indicated. Clinical inertia is due to at least three problems: Overestimation of care provided; use of “soft” reasons to avoid intensification of therapy; and lack of education and training aimed at achieving therapeutic goals. It is an important reason for not attaining treatment goals in RH. Therapeutic drug monitoring has a potential for monitoring and tailoring treatment.

#### Lifestyle factors

Alcohol, obesity, dietary sodium, physical inactivity, and dietary patterns all contribute to RH.

#### Drugs and other substances with a potential to induce or exacerbate elevated BP and HT

This includes NSAIDs, oral contraceptives, sympathomimetics, cyclosporine, tacrolimus, erythropoietin, VEGF inhibitors,

alcohol, cocaine, amphetamines, antidepressants, glucocorticoids and mineralocorticoids, oral contraceptives, and hormone replacement.

### Diagnosis and management of secondary HT

#### Primary aldosteronism

Primary aldosteronism is particularly common with a prevalence rate of approximately 20% in patients with confirmed RH.<sup>[9]</sup> Screening for primary aldosteronism should be conducted using the plasma aldosterone concentration to plasma renin activity ratio from a morning blood sample obtained after the patient has been in a seated position for at least 30 min before sampling.<sup>[1]</sup> Unilateral laparoscopic adrenalectomy offers a complete cure in >50% or improvement ( $\approx$ 50%) in BP control. Half of the unilateral disease is caused by aldosterone-producing adenoma, and unilateral hyperplasia is rare. Mineralocorticoid receptor antagonists (MRA) such as spironolactone or eplerenone give good control of BP in subjects with bilateral disease (idiopathic hyperaldosteronism).<sup>[10]</sup>

#### Renal parenchymal disease

CKD is both a cause and a complication of poorly controlled HT.<sup>[1]</sup> Target BP goal of <130/80 is more often attained in stage 1 CKD (49.5%). The control rate drops to 30.2% at stage 4. The overall control rate in CKD as a whole is 44.6%, even though antihypertensive medications are used more frequently in CKD. When the ESC target of  $\leq$ 140/90 mmHg was used, it was attained in only 66.5%.<sup>[11]</sup> Loop diuretics are often needed as the renal function declines.

#### Renal artery stenosis

Secondary causes form 12.7% of the total in a HT specialty clinics referral analysis. Occlusive renovascular disease formed 35% of this subgroup.<sup>[12]</sup> Non-dipper BP profile, sudden deterioration of renal parameters especially after RAS inhibitors and abrupt progression of HT mandate screening for renal artery stenosis. Atherosclerosis is the etiology in majority of the cases of renal artery stenosis. Other less common causes including a variety of fibromuscular dysplasias, renal artery dissection or infarction, Takayasu arteritis, radiation fibrosis, and renal artery obstruction from aortic endovascular stent grafts should be considered and ruled out.<sup>[1]</sup> In general, ACE inhibitor or ARB therapy is tolerated well by the majority of patients with renovascular disease without adverse renal effects. The clinician should be aware that a small number (10–20%) will develop an unacceptable rise in serum creatinine. Volume depletion and presence of bilateral renal artery stenosis could be the trigger for this rise and should be avoided or corrected.<sup>[1]</sup> The pendulum for renal artery stenting (RAS) for the treatment of RH has swung from broad endorsement to calls for an almost complete moratorium. This extreme swing has been due to the highly publicized release of two RAS trials (ASTRAL and cardiovascular outcomes with renal artery lesions [CORAL]). However, these studies did not focus on the population that

would benefit most from RAS, i.e., hemodynamically significant renal artery stenosis with RH. RAS took a backseat after ASTRAL and CORAL trials. However, a subset of medically treated patients with renal artery stenosis may benefit with RAS and includes those who have worsening HT, renal insufficiency, or fluid overload (“flash pulmonary edema”). These are conditions with higher risks of death. RAS is also a good option for patients with atherosclerotic severe renal artery stenosis (either >70% angiographic diameter or 50–70% stenosis with hemodynamic confirmation of lesion severity) with true resistant HT or with HT and intolerance to medication. SCAI expert consensus statement for RAS appropriate use 2014 gave Class II a: LOE B for RAS in accelerated, resistant, or malignant HT. A mortality benefit of revascularization was seen in the *post hoc* analysis of the CORAL trial data for atherosclerotic renal artery stenosis in patients without proteinuria compared with medical therapy.<sup>[13]</sup> A short period of pressure elevation after revascularization is a reliable predictor for effective BP reduction in the long term.<sup>[1]</sup>

#### Pheochromocytoma/paraganglioma

Even though the classical feature is paroxysmal HT, elevated BP levels may be sustained in up to 50% of high norepinephrine-producing tumors. Orthostatic fluctuations in BP should lead to a suspicion of epinephrine-predominant tumors. The symptoms of headache, palpitations, pallor, and piloerection (“cold sweat”) in patients should be sought for and the index of suspicion should be high.<sup>[1]</sup> Measurement of circulating catecholamine metabolites is the screening test of choice for pheochromocytoma/paraganglioma.

Cushing’s syndrome, coarctation of the aorta, and other rarer causes of secondary HT should not be forgotten during evaluation.

#### Evaluation of RH

The focus for evaluation should be on confirmation of true treatment resistance, identification of causes contributing to resistance (including secondary causes of HT), and documentation of complications of the hypertensive disease process. Algorithm for evaluation as per the AHA scientific statement 2018 on RH is given in Table 1.<sup>[1]</sup>

#### Management of RH

Management approach can be broadly divided into lifestyle interventions, pharmacotherapy, and device therapy.

#### Lifestyle interventions

Weight reduction, lowering salt intake, DASH diet, and exercise are traditional lifestyle modifying measures. Alternative measures include acupuncture and yoga. Other modalities, including transcendental meditation, device-guided slow-breathing, and isometric handgrip exercise, have been tried with varying success. Isometric handgrip, typically performed for 12 min 3–5 times/

**Table 1:** Treatment approach to resistant hypertension as per aha 2018 guidelines

week, lowers BP by 5.2/3.9 mmHg.<sup>[1]</sup> The role of improving sleep quality and avoiding environmental triggers such as cold, noise, and pollution appears promising.

### Pharmacological approaches

#### Diuretics

For true RH, the first approach would be to optimize diuretics. MRAs (spironolactone 25–50 mg daily or eplerenone 50–100 mg daily) are the current mainstay. Increasing the dose of the existing diuretic or switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide) should be done. A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is <30 ml/min. The use of spironolactone for resistant HT should usually be restricted to patients with an eGFR  $\geq$ 45 ml/min and a plasma potassium concentration of  $\leq$ 4.5 mmol/L. Amiloride (10–20 mg/day) has been shown to be as effective as spironolactone (25–50 mg daily) in reducing BP in the PATHWAY-2 study. The PATHWAY-2 study also evaluated bisoprolol (5–10 mg/day) or doxazosin modified release (4–8 mg/day) as alternatives to spironolactone. Thus, bisoprolol and doxazosin though not as effective as MRA have an evidence base for the treatment of resistant HT when spironolactone is contraindicated or not tolerated.<sup>[14]</sup> Frusemide or bumetanide should be given twice or thrice daily as they have a shorter duration of action. Once-daily dosage of frusemide is associated with intermittent natriuresis and consequent sodium retention mediated by RAS increase. Torsemide has a longer duration of action and may be given once or twice daily. The 2018 ESC/ESH recommendations on RH are given in Table 2.<sup>[14]</sup>

Choice of other antihypertensives is also important. The more potent drug of each class should be chosen. Among ARBs, azilsartan in ABPM studies has been shown to have further 4–8 mmHg reduction in SBP compared to valsartan, olmesartan, or ramipril.<sup>[1]</sup> Long-acting formulations of nifedipine may have better BP lowering effect than amlodipine but at the expense of increasing edema.

Divided doses and nocturnal or bedtime dosing may be, especially, useful. Additional drugs that can be used depend

on the sympathetic drive and tolerability. B-blockers, centrally acting drugs clonidine or moxonidine, can be tried. Clonidine tablets should be used with caution due to the risk of rebound HT. The next line of drugs that can be utilized are hydralazine and minoxidil. However, minoxidil increases sympathetic tone and sodium avidity and a background B-blocker and diuretic therapy may be needed. An algorithm for managing RH as per the AHA 2018 guidance is given in Table 3.<sup>[1]</sup>

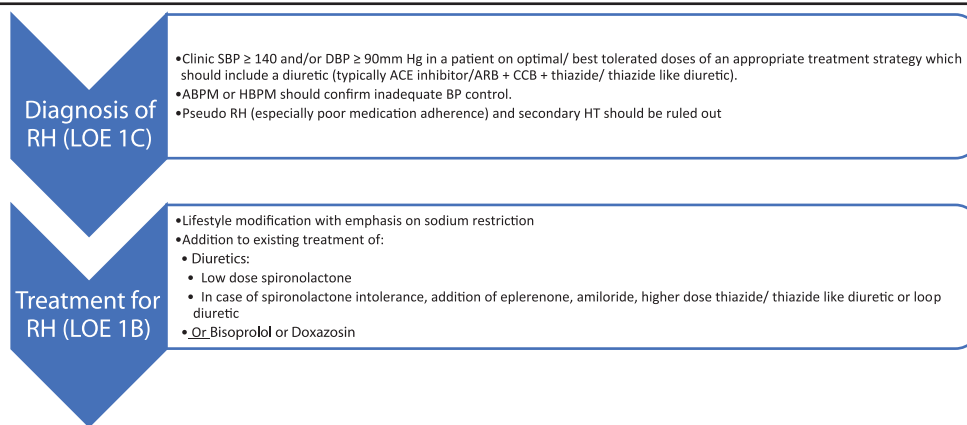
### Renal Denervation (RDN)

Although most of the early studies showed great promise and generated considerable interest, these were uncontrolled and did not use ABPM. The first sham-controlled prospective randomized study in the field of renal ablation therapy (SYMPPLICITY HTN-3) showed little to no effect of RDN therapy in a severely drug-resistant population setting.<sup>[1]</sup> There may be many reasons why SYMPPLICITY HTN-3 failed to demonstrate the expected benefit, one being possible incomplete denervation. There is a greater concentration of nerves in the proximal and middle segments of the renal artery, and the nerves in the distal segment lie closer to the lumen (30% of proximal vessel fibers are found between 4 and 9 mm from the lumen, which is too far to be reached by low-energy radiofrequency ablation). Other possible causes of the negative result could be the difference in population cohorts and Hawthorne effect. HT-1 had no controls, and HT-2 was not sham controlled. The greater effect on BP control in the control population may be at least partially explained by the fact that they were participants in the trial.

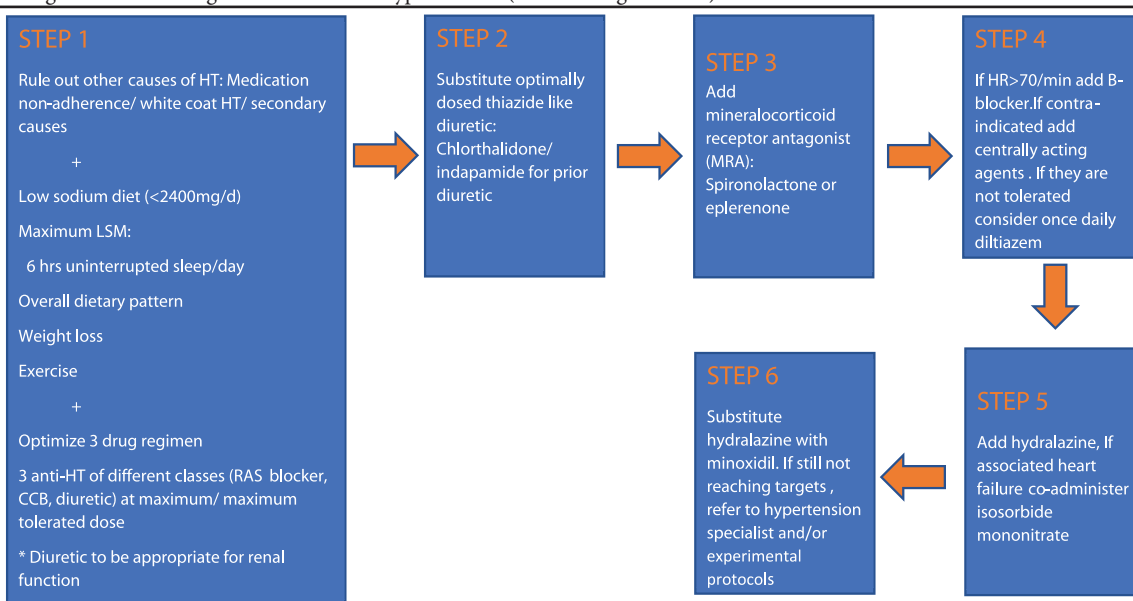
### Future for RDN

Although the efficacy of RDN is under serious debate, safety in the short term and medium term is well established. There is a low risk of procedural complications. SPYRAL HT global clinical trial program using symplicity spyril multielectrode RDN catheter having multiple circumferential electrodes that can deliver radiofrequency energy to multiple segments of the vessel wall at the same time and the DENERTHTN trial showed

**Table 2:** 2018 ESC/ESH recommendations on RH



**Table 3:** Algorithm for management of resistant hypertension (AHA 2018 guidelines)



that RDN may still be effective. Non-invasive RDN using several piezoelectric transducers to direct high-frequency sound waves causing thermal effects that lead to highly specific ablation of target tissue is also in the pipeline. Transcatheter perivascular alcohol denervation provides an interesting safety/efficacy profile. RADIOSOUND-HT study randomized patients with RH to receive either RDN of the main renal arteries (RFM-RDN) or radiofrequency RDN of main renal arteries, side branches and accessories (RFB-RDN) or endovascular ultrasound based RDN of the main renal artery. The results indicated that, in RH, RDN using the Paradise endovascular ultrasound RDN system resulted in greater reduction in ambulatory SBP at 3 months compared with RFM-RDN but not RFB-RDN. This difference may be due to deeper penetration of energy and more complete sympathetic ablation.<sup>[15]</sup>

**Baroreceptor activation therapy**

The Mobius HD carotid bulb expansion device is a small endovascular implantable device that works by stretching the carotid artery at the bulb, thereby activating baroreceptors to lower BP.<sup>[1]</sup> It is sympathomodulatory, and an increase in the carotid bulb strain causes durable amplification of baroreceptor feedback and BP reduction. The CALM-FIM\_EUR study has recently demonstrated in patients with RH that endovascular baroreflex amplification with the Mobius HD device substantially lowered BP with an acceptable safety profile. CALM-FIM\_US is an ongoing study.<sup>[1]</sup>

**Devices in the pipeline for RH**

*Central arteriovenous anastomosis*

Central AV iliac anastomosis with ROX AV coupler targets mechanical aspects of circulation and lowers BP through effectively

reducing the arterial volume and systemic vascular resistance. There is a 30% incidence of ipsilateral venous stasis. Risk of high output states is low. There are no long-term safety data.

#### *Carotid body ablation*

Unilateral carotid body ablation reduces sympathetic vasomotor tone without affecting respiratory drive. There is proof of concept studies with surgical ablation in RH. Endovascular approach for the same is being explored. It appears effective only in those with high carotid body tone, and screening for which is, therefore, essential before employing this modality of management. Endovascular approach has the challenges of difficulty in accessing the target and damage to adjacent structures.

#### **Deep brain stimulation**

This is a sympathomodulatory measure. Electrical stimulation of the dorsal and ventrolateral periaqueductal gray region within the midbrain reduces the BP through mechanisms not clearly elucidated. This technology was primarily developed for movement disorders and chronic pain syndromes. However, there are isolated reports of lowering of BP independently. It has limited efficacy/safety data.

#### **Drugs in the pipeline targeting RAS and NP systems**

Finerenone (MRA), osilodrostat (LCI 699- 11B hydroxylase inhibitor), RhACE2 (ACE2 activator), RB 150 (aminopeptidase A inhibitor), valsartan-sacubitril (dual ARB-neprilysin inhibitor already approved in heart failure), daglutril (dual ECE-neprilysin inhibitor), and PL3994 (NP A agonist) are some of the medications in the pipeline for RH. VIP receptor 2 agonists, intestinal Na/H exchange inhibitions, DBH inhibition, and vaccines against Ang-II are also under early trial stages.

#### **Pharmacogenomics**

The response to equivalent doses of ACE inhibitors varies considerably among individuals. An ACE gene polymorphism (287 Bp insertion in Intron16) accounts for approximately 50% of the genetic variance in serum ACE levels. Approximately 20% of individuals have the 287 Bp insertion. Caucasian patients with the 287 Bp insertion have a poor response to ACE-inhibitors.

#### **Ten Practical Points on RH**

1. Exclude pseudo resistance. Evaluate for white coat effect, pseudo-HT. Use ABPM and HBPM.
2. Lifestyle factors are important. Diet and exercise are important. Avoid hidden sources of salt.
3. Check medications: Adherence, persistence, optimum dose, and use of right combinations.
4. Look for associated conditions and secondary HT: Sleep study, renal artery Doppler, hyperaldosteronism.
5. Diuretics: Given in divided doses. Spironolactone/

eplerenone very important.

6. Use of more potent drugs of each class.
7. Bedtime dosage.
8. Old may still be gold: Moxonidine, hydralazine, minoxidil.
9. RAS in selected cases.
10. RDN: Down but not totally out.

#### **Conclusions**

Resistant HT remains a challenging condition with poor prognosis. It includes high-risk patients who need effective strategies. ABPM and HBPM are a necessary part of workup and control of variables such as modifications in lifestyle and treatment regimen as well as ascertaining adherence to treatment is fundamental. Pharmacological treatment with diuretics, especially MRA, remains the mainstay but is often unsuccessful in reaching target goals. RDN remains worthy of continuing investigation.

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