

Refractory versus resistant hypertension: Novel distinctive phenotypes

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Resistant hypertension (RHTN) is relatively common with an estimated prevalence of 10-20% of treated hypertensive patients. It is defined as blood pressure (BP) >140/90 mmHg treated with ≥ 3 antihypertensive medications, including a diuretic, if tolerated. Refractory hypertension is a novel phenotype of severe antihypertensive treatment failure. The proposed definition for refractory hypertension, i.e. BP >140/90 mmHg with use of ≥ 5 different antihypertensive medications, including a diuretic and a mineralocorticoid receptor antagonist (MRA) has been applied inconsistently. In comparison to RHTN, refractory hypertension seems to be less prevalent than RHTN. This review focuses on current knowledge about this novel phenotype compared with RHTN including definition, prevalence, mechanisms, characteristics and comorbidities, including cardiovascular risk. In patients with RHTN excess fluid retention is thought to be a common mechanism for the development of RHTN. Recently, evidence has emerged suggesting that refractory hypertension may be more of neurogenic etiology due to increased sympathetic activity as opposed to excess fluid retention. Treatment recommendations for RHTN are generally based on use and intensification of diuretic therapy, especially with the combination of a long-acting thiazide-like diuretic and an MRA. Based on findings from available studies, such an approach does not seem to be a successful strategy to control BP in patients with refractory hypertension and effective sympathetic inhibition in such patients, either with medications and/or device based approaches may be needed.

Alosterone | antihypertensive treatment failure | treatment resistance | sympathetic activity | volume dependent

Introduction

With the introduction of antihypertensive pharmacological treatment in the last century, evidence emerged that the blood pressure (BP) response to treatment varies between individuals and that some patients require more medications to control their BP than others. The terms “refractory” and “resistant” hypertension were first used more than six decades ago to characterize such patients. [1, 2]

Initially, both terms were interchangeably applied to identify patients with difficult-to-treat hypertension. However, in 2008 the American Heart Association issued a scientific statement to provide a consensus for the definition for resistant hypertension (RHTN). [3] Recently, the term refractory hypertension has been proposed to refer specifically to patients failing maximal antihypertensive treatment defined as lack of BP control despite treatment with at least 5 different antihypertensive agents, including a diuretic and a mineralocorticoid receptor antagonist (MRA). [4]

Definition

Resistant hypertension

As defined in a scientific statement by the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research on Resistant Hypertension, RHTN

is defined as uncontrolled BP (>140/90 mmHg) despite use of ≥ 3 antihypertensive medications, including a diuretic, if tolerated. [3]

Refractory Hypertension

Refractory hypertension has been suggested to refer specifically to patients who are failing maximal antihypertensive treatment. This recently proposed definition is based on failure to control BP >140/90 mmHg despite use of ≥ 5 different antihypertensive medications, including a long-acting thiazide-like diuretic, and a mineralocorticoid receptor antagonist. [5, 6]

Prevalence

Resistant hypertension

The prevalence of RHTN from various cohorts, including outcome-based trials, registry data, and population studies is estimated to be approximately 10-20% of patients being treated for hypertension. For example, de la Sierra et al. reported the prevalence of RHTN as 12.2% of treated hypertensive patients included in The Spanish Ambulatory Blood Pressure Monitoring Registry [7]. Sim et al. reported the prevalence of RHTN as 12.8% of all hypertensive patients and 15.3% of hypertensive patients receiving treatment within the Kaiser Permanente Southern California healthcare system based on review of electronic medical records. [8] Analyses of National Health and Nutrition Examination Survey (NHANES) data, drawn from representative samples of the adult, non-institutionalized, civilian population, have estimated the prevalence of RHTN at 8.9% of the US hypertensive population from 2003-2008. Interestingly, a time-sequence comparison of NHANES data from 1998 through 2008 suggests that, unlike hypertension, apparent RHTN is becoming more prevalent and increased from 15.9% (1998-2004) to 28.0% (2005-2008) of treated patients ($P < 0.001$), likely due, in large part, to aging and increasing obesity rates in the general population. [9, 10]

Refractory Hypertension

The prevalence of refractory hypertension has been defined in a limited number of studies. In a prospective evaluation, Dudenbostel et al. reported the prevalence of refractory hypertension as 2.7% of patients referred to a hypertension specialty clinic for uncontrolled RHTN, based on having never achieved blood pressure control with use of ≥ 5 or more medications, including chlorthalidone 25 mg daily and

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spironolactone 25 mg daily after 3 follow up visits confirmed by 24-hr ambulatory BP monitoring. [6]

Acelajado et al. reported in a retrospective analysis of Caucasian and Black patients referred to a hypertension specialty clinic that 9.5% of patients with RHTN never achieved BP control despite use of an average of six different antihypertensive medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blocker, beta blocker, calcium channel blocker, diuretics, mineralocorticoid receptor antagonists, vasodilators, and central adrenergic inhibitors. [4] In this analysis, 82.8 % of patients were treated with both chlorthalidone and spironolactone. Similarly, Modolo et al. reported a prevalence of 31% of refractory HTN among Brazilian patients with true RHTN, with 72% of the refractory patients being treated with spironolactone in addition to a diuretic. [11]

Based on a cross-sectional analysis of data of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large, national, community-based cohort, Calhoun et al. estimated the prevalence of refractory hypertension as 3.6% of participants with apparent RHTN [5]. In that study, refractory hypertension was defined as lack of BP control while taking ≥ 5 antihypertensive medications. However, only 18% of patients considered as being refractory were being treated with an MRA.

In conclusion, more studies using a standardized definition of refractory hypertension, that is patients who are failing multiple-drug regimens that include both a diuretic and a mineralocorticoid receptor antagonist, are needed.

Pseudo-resistant and pseudo-refractory hypertension

Resistant hypertension

The term apparent RHTN is used when common causes of pseudo-resistant hypertension, such as inaccurate BP measurements, medication non-adherence, under treatment, and white coat effect have not been excluded (Table 1). Accounting for these causes of pseudo-resistant or pseudo-refractory hypertension will provide more accurate estimates of prevalence rates of true RHTN and true refractory hypertension. It is estimated that combined causes of pseudo-resistant hypertension likely account for approximately half of cases of apparent RHTN. [12]

Table 1. Causes of pseudo-resistant hypertension

| Causes of pseudo-resistant hypertension |
|---|
| <ul style="list-style-type: none"> • White coat effect • Inaccurate blood pressure measurement • Medication non-adherence • Under treatment |

White coat effect

White coat effect is common in patients with RHTN and is defined as uncontrolled BP in clinic but controlled at home by 24-hr ambulatory BP monitoring. De la Sierra and colleagues found a white coat effect in 37.5% of patients with apparent RHTN in a large Spanish cohort with 8295 patients. [7] Similarly, Muxfeldt et al. and Modolo et al. reported that 37% and 39%, respectively, in a Brazilian cohort had white coat RHTN. [11, 13]

Role of blood pressure measuring technique

Poor BP measuring technique is a common underlying cause for falsely diagnosed RHTN and refractory hypertension. Studies have shown that poor BP measuring technique accounts for a high prevalence of falsely diagnosed RHTN or refractory hypertension.

[3, 14] Bhatt et al. recently determined the prevalence of falsely diagnosed uncontrolled RHTN due to poor BP measuring technique. [15] In this retrospective analysis of 130 patients referred to a hypertension clinic, routinely measured clinic triage BP readings were then compared to BP measurements obtained by physician examiners using an automated, unattended BP device. The investigators found that 33% patients had been falsely diagnosed as having uncontrolled RHTN as compared to the routine BP assessments. [15]

Medication non-adherence

Medication non-adherence may be the most common cause of apparent RHTN. In an evaluation of patients with RHTN referred for renal denervation (RDN), Jung et al. reported that 53% of patients were partially non-adherent and 30% were not taking any of the prescribed antihypertensive medications. In this study, levels of antihypertensive agents or their metabolites were measured in the urine. [16] Similarly, Štrauch et al. found non-adherence among a cohort of patients with RHTN to be 47%, also having directly measured medication levels or its metabolites. [17]

Combined causes of pseudo-resistant hypertension

Grigoryan et al. estimated the prevalence of combined causes of pseudo-resistant hypertension, such as white coat effect, medication non-adherence, or use of suboptimal treatment dosages in the same cohort of 140 primary care patients. Of these, 22% were controlled on 24-hr ambulatory BP monitoring, 29% were uncontrolled and non-adherent, leaving only 49% adherent to their medications and having uncontrolled hypertension by 24-hr ambulatory BP monitoring. In this study, prescribed antihypertensive medications and doses were documented, all study participants underwent 24-hr ambulatory BP monitoring, and medication adherence was determined with use of electronic monitoring [12]. Overall, one-half of the RHTN were attributed to white coat effect and poor medication adherence, and all of the remaining patients with RHTN were on apparently suboptimal drug combinations and/or dosages. [12]

Another estimate of combined causes of pseudo-resistant hypertension comes from population-based data of individuals in a large, healthcare organization in Israel. [18]

Weitzman et al. reported that among the 172 432 hypertensive patients, 35.9% had uncontrolled hypertension.[18] Of these, almost all were undertreated, 21% received less than maximal dosages of prescribed medications, 9% were not receiving a diuretic, 48% had been dispensed less than 3 antihypertensive agents, and 20% had been dispensed none of the prescribed agents. After exclusion of these patients, only 2.2% of the patients with uncontrolled hypertension met the criteria for RHTN. These findings suggest that uncontrolled BP in treated patients is much more likely attributable to the combination of undertreatment and poor medication adherence.

Similar findings of undertreatment were documented by Hwang et al. who analyzed trends in antihypertensive medication use among US patients with RHTN over a 6-year period. [19] Using a large, national claims database, which contains medical and prescription claims data that is representative of patients covered by employer-based insurance programs, the authors found that among patients with RHTN, the use of chlorthalidone and spironolactone, remained extremely low. In this study of 18 to 65 years old patients with ≥ 6 months of continuous enrollment, a hypertension diagnosis, and ≥ 1 episode of overlapping use of ≥ 4 antihypertensive drugs were included. Patients with heart failure were excluded.

The investigators found that despite the recognized preferential use of chlorthalidone over hydrochlorothiazide, chlorthalidone use had increased only by 2.6% between 2008 and 2014 in patients with RHTN. Overall, by the end of 2014, 92.9% of patients were still receiving hydrochlorothiazide versus the 6.4% receiving chlorthalidone. Furthermore, despite the clearly established benefit of spironolactone for treatment of RHTN, only $\approx 10\%$ of patients were prescribed spironolactone. In a separate study, Fadl Elmula et al. further demonstrated the effectiveness of optimized pharmacological therapy for treatment of RHTN. [20] After excluding non-adherent individuals, patients with RHTN were randomized to RDN or to adjustment and intensification of pharmacological therapy guided by measurement of impedance cardiography to estimate volume status. In this small study, 9 patients were randomized to titration of drug therapy and 10 patients randomized to RDN, the authors demonstrated that guided medication adjustment and intensification was superior to RDN as indicated by reduction in systolic and diastolic BP and changes in 24-hr ambulatory BP levels at 6-month follow-up evaluations.

These findings further support the contention that apparent RHTN is often attributable to poor medication adherence and/or undertreatment. It highlights the need for better education of practitioners on how to optimize antihypertensive regimens, including specifically, use of a long-acting thiazide-like diuretic and an MRA. [3, 21]

| Resistant Hypertension | | Refractory Hypertension |
|------------------------|-----------------|-------------------------|
| 10-20% | Prevalence | 5% |
| Older | Age | Younger |
| Male | Gender | Female |
| Black | Race | Black |
| ↑ | Aldosterone | ↔ |
| ↑ | S _{at} | ↔ |
| ↑ AHI | OSA | Unknown |
| ↑ | Obesity | ↑ ↑ |
| ↑ | Diabetes | ↑ ↑ |
| Volume Dependent | Mechanism | ↑ Sympathetic Activity |
| ↑ | CV Risk | ↑ ↑ |

Figure 1. Factors associated with refractory hypertension compared with controlled resistant hypertension.

Refractory hypertension

To what extent the white coat effect, poor BP measurement technique, and medication non-adherence contribute to apparent refractory hypertension is only partially known. Likely the occurrence of these causes of pseudo-refractory hypertension will be at least as common as in patients with RHTN. Under treatment is, by definition, excluded based on an obligatory use of ≥ 5 different antihypertensive medications including a long-acting thiazide-like diuretic and an MRA.

In a recent study by Siddiqui et al. the white coat effect was uncommon in patients with refractory hypertension. In this prospective evaluation of 34 patients with apparent refractory hypertension, of whom 31 had adequate 24-hr ambulatory BP readings, a prominent white coat effect was present in only 6.5% of patients with refractory hypertension. [22]

Mechanisms

Mechanisms of Resistant hypertension

RHTN is thought to be attributable in large part to excess fluid retention. This pathophysiologic link is suggested by the pivotal role that intensification of diuretic therapy plays in achieving BP control in patients on multiple antihypertensive medications [23, 24] (Figure 1). Studies have shown that intensification of diuretic therapy, guided by impedance cardiography to measure thoracic fluid content [25, 26] or by indirect biochemical indices of intravascular volume such as natriuretic peptide levels, [25] significantly improves BP control. The etiology of this excess fluid retention is no doubt multifactorial, including older age, obesity, chronic kidney disease (CKD), black race, hyperaldosteronism [25, 27], and excessive dietary sodium intake [28].

Mechanisms of Refractory Hypertension

Reasons for failure of antihypertensive therapy in patients with refractory hypertension remain poorly understood, but heightened sympathetic activity is widely viewed as a major contributor to treatment failure (Figure 1). Clinical studies suggest that refractory hypertension is less likely to be volume-dependent and more likely to be neurogenic in etiology. Patients with refractory hypertension seem not to have excess fluid retention compared to patients with RHTN. These findings are supported by results from impedance cardiography showing that thoracic fluid content is reduced in patients with refractory hypertension [6]. One prospective study by Dudenbostel et al. showed that overactivation of the renin-angiotensin-aldosterone system and rates of hyperaldosteronism are less likely to play a role in patients with refractory hypertension compared to patients with resistant hypertension in general. In that study, Dudenbostel et al. also showed that lifestyle factors such as high dietary sodium intake indexed by 24-hr urinary sodium excretion are less prevalent in patients with refractory compared to RHTN. In that study, patients with RHTN had a significantly higher sodium intake and lower clinic and ambulatory BP levels on less antihypertensive agents. Similar observations were made in a cross-sectional evaluation of a cohort of Brazilian patients with refractory hypertension, confirming that common causes of RHTN are less likely to play a role in causing refractory hypertension. [11] Furthermore, in contrast to patients with RHTN, individuals with refractory hypertension, by definition, are failing intensive therapy, including use of combined a long-acting thiazide-like diuretic and an MRA. [6] Combined, these findings argue against volume overload as a major cause of refractory hypertension.

In their prospective evaluation of patients with refractory hypertension, Dudenbostel et al. assessed indices of sympathetic

tone. [6] The investigators found significantly higher clinic and 24-hr ambulatory heart rates, 24-hr excretion of normetanephrines, and higher systemic vascular resistance measured by impedance cardiography in patients with refractory hypertension compared to patients with controlled RHTN. These findings point to greater sympathetic output. However, the assessment of direct sympathetic output is difficult and more data are needed. If confirmed by additional studies, this would represent an important mechanistic difference in that refractory hypertension more of a neurogenic etiology as opposed to being a volume dependent, typical of resistant hypertension. Such a distinction in mechanisms would have important implications in terms of treatment. Patients with refractory hypertension may not benefit from a continued titration of diuretic therapy, but rather, from sympatholytic therapies. If so, the findings highlight the need for more effective sympatholytic interventions. [29]

Characteristics and Comorbidities

Resistant hypertension

Compared to patients with more easily controlled hypertension, patients with RHTN are more likely older, Black, and obese. Comorbidities commonly associated with RHTN include chronic kidney disease, type 2 diabetes, hyperaldosteronism, obstructive sleep apnea, and cardiovascular (CV) and cerebrovascular disease. [7, 8, 30-32]

Refractory Hypertension

Compared to patients requiring multiple medications, but whose BP is controlled, i.e., controlled RHTN, patients with refractory tend to be more often of black race, female, and younger. [4-6, 11]

Comorbidities

Comorbidities associated with RHTN compared to controlled RHTN have varied depending on the cohort analyzed and how refractory hypertension was defined.

Acelajado et al. reported that prior history of congestive heart failure and stroke was increased in patients with refractory hypertension.[4] Calhoun et al. reported microalbuminuria and type 2 diabetes to be more commonly associated with refractory hypertension. [5] Dudenbostel et al. and Modolo et al. found significant higher rates of congestive heart failure (CHF) and left ventricular hypertrophy, respectively [6, 11].

Prognosis

Resistant hypertension

As would be expected with a history of poorly controlled, often severe hypertension, patients with RHTN have a worse CV disease prognosis, including coronary heart disease, stroke, CHF, peripheral artery disease, and CKD compared to patients with more easily controlled hypertension. [3, 7, 9, 10, 33-35]

In a post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which included 1870 participants with RHTN, Muntner et al. found that compared with study participants without RHTN, participants with RHTN had a 44%, 57%, 23%, 88%, 95%, and 30% higher risk of incident coronary heart disease, stroke, peripheral artery disease, CHF, end-stage renal disease, and all-cause mortality, respectively, during the almost 5-year duration of the study after adjustment for multiple traditional risk factors, such as age, smoking, type 2 diabetes, and low-density lipoprotein cholesterol.[31]

The ALLHAT study design did not require diuretic use to define RHTN; however, in the sensitivity analysis, which was restricted to subjects with diuretic treatment, RHTN remained

significantly associated with the specified clinical outcomes, except for stroke and all-cause mortality.

Diaz et al evaluated the association of 6 different healthy lifestyle factors (normal waist circumference, physical activity ≥ 4 times/week, nonsmoking, moderate alcohol ingestion, high Dietary Approaches to Stop Hypertension diet score, low sodium-to-potassium ratio) and risk of CV complications and all-cause mortality among the 2043 participants with RHTN in the REGARDS study.[36] After a median follow-up of 4.5 years, compared with study participants with generally unhealthy lifestyles (i.e., presence of ≤ 1 healthy lifestyle factor), those with healthy lifestyles (i.e., presence of all 6 healthy lifestyle factors) had a substantially lower risk of CV events. Overall, a greater number of healthy lifestyle factors was associated with a lower risk of CV events, CV mortality, and all-cause mortality. Among the 6 healthy lifestyle factors, physical activity and nonsmoking were the most favorable in terms of prognosis. Patients with RHTN likewise are more likely to develop CKD [31]. Epidemiological studies have shown that patients with CKD have a much higher prevalence of RHTN than general hypertensive populations and that patients with RHTN and CKD have an increased prevalence of CV diseases compared with patients without RHTN. [8, 37] Recently, two large multicenter, prospective studies further delineated the prognostic significance of RHTN in individuals with CKD. De Beus et al. evaluated 788 patients with CKD with a mean estimated glomerular filtration rate (eGFR) of 38 ± 15 mL/min per 1.73 m². [38] Around 34% of these patients had RHTN. After a median follow-up of 5.3 years, nearly 17% of the individuals with RHTN had experienced a CV event, including myocardial infarction, ischemic stroke, or death, and 27% had developed end-stage renal disease.

Compared with individuals without RHTN, those with RHTN had a 1.5-fold and 2.3-fold higher risk of composite CV events and end-stage renal disease, respectively. Analysis of data from the Chronic Renal Insufficiency Cohort (CRIC) Study indicated that among the 3367 patients CKD with an eGFR of 20 to 70 mL/min/ 1.73 m², the prevalence of RHTN was 40.4%. [39] Every 5 mL/min/ 1.73 m² decrease in estimated glomerular filtration rate was associated with a 14% higher risk of having RHTN. Compared with those without RHTN, individuals with RHTN had a poorer prognosis, with a 38%, 28%, 66%, and 24% higher risk of experiencing a CV complication, renal complication, incident heart failure, or death, respectively. Despite some differences in how RHTN was defined between the above studies, these recent longitudinal analyses are important in consistently demonstrating that patients with RHTN, especially those with concurrent CKD, have substantially impaired CV and renal prognosis compared with patients with more easily controlled hypertension.

Not surprisingly, given this increased CV risk, having RHTN is associated with an overall higher mortality compared to non-RHTN [31, 32, 40, 41].

Refractory Hypertension

Like RHTN, the CV prognosis of patients of patients with refractory hypertension is no doubt impaired, but to date, longitudinal assessments quantifying that risk have not been done.

Treatment

Resistant hypertension

Treatment of RHTN is largely predicated on intensification of diuretic therapy after failing to control BP with use of a standardized three-drug regimen of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, a calcium channel blocker, and thiazide-like diuretic. Toward that end,

combined use of a long-acting thiazide-like diuretic and an MRA can provide substantial add-on antihypertensive benefit.

This recommendation is based on studies demonstrating the effectiveness of the MRA spironolactone as a fourth antihypertensive agent for treatment of RHTN and on studies indicating superiority of chlorthalidone over hydrochlorothiazide (HCTZ) in terms of antihypertensive benefit. For example, Gaddam et al. reported that patients with RHTN often have evidence of excess fluid retention when being treated with HCTZ alone. However, with treatment of chlorthalidone and spironolactone, the underlying fluid retention could be overcome with substantial improvement in BP [24, 25].

Over the last decade, numerous studies have demonstrated the efficacy of the MRA spironolactone for treatment of RHTN. [42-44]

These studies, however, were often limited in being single center studies of small cohorts or having been done in an unblinded and uncontrolled fashion. These limitations were overcome with the "PATHWAY-2 study. [21] In a rigorous, double-blind placebo-controlled, cross-over evaluation of a large cohort of patients with confirmed RHTN, Williams et al. reported that spironolactone, as a fourth antihypertensive agent, was superior to doxazosin and bisoprolol based on reduction of home systolic BP. [21] The PATHWAY-2 findings are clinically important in that this study clearly confirms that spironolactone is the most appropriate fourth agent for treatment of RHTN.

The preferential benefit of a MRA for treatment of RHTN is consistent with a large body of literature demonstrating that RHTN is commonly characterized by varying degrees of hyperaldosteronism and accompanying intravascular fluid retention.

In the PRAGUE-15 study, a randomized, open-label, multicenter evaluation, intensification of pharmacological therapy, including use of spironolactone, was compared with RDN for treatment of RHTN to evaluate the efficacy of RDN versus pharmacotherapy. [45] The cohort consisted of 106 patients with confirmed RHTN based on documentation of medication adherence, exclusion of secondary causes of hypertension, and exclusion of white coat effect by 24-hour ambulatory BP monitoring. At 6- and 12-months follow-up, the 2 interventions had induced comparable reductions in 24-hour ambulatory systolic BP. [45]

In the Renal Denervation for Hypertension (DENERHTN) trial, intensification of pharmacological therapy alone was compared with RDN in combination with intensification of pharmacological therapy in patients with confirmed RHTN. [46] After 6-month follow-up in this open-label study design, both interventions had significantly reduced 24-hour systolic BP, but RDN had provided an additional 5.9 mmHg reduction compared

with intensification of pharmacological therapy alone. The divergent results of the PRAGUE-15 Study and the DENERHTN trial need to be reconciled with further evaluations, but the findings of the 2 studies suggest that RDN and intensified pharmacological treatment with use of spironolactone will be complimentary and that, on an individual patient basis, both will be important options for overcoming treatment resistance.

Refractory Hypertension

How to better treat refractory hypertension has not yet been determined. These patients are failing all commonly used classes of antihypertensive agents, including intensive diuretic therapy with a long-acting thiazide diuretic and an MRA. Preliminary findings suggest that true antihypertensive failure may be partially neurogenic in etiology. If so, use of effective sympatholytic therapies, either pharmacological or device-based such as RDN, may be indicated, but studies specifically testing such benefit in this cohort have not yet been done. [4, 5, 6, 11].

Conclusion

Refractory hypertension is a novel phenotype of antihypertensive treatment failure defined by uncontrolled BP on five or more antihypertensive medications, including a long-acting thiazide diuretic and an MRA. This phenotype seems to be rare, comprising only about 5% of patients referred to a hypertension specialty clinic for uncontrolled RHTN. Like RHTN in general, refractory hypertension is more common in Blacks, patients with obesity, and type 2 diabetes.

However, compared to RHTN, patients with refractory hypertension tend to be younger and more often female. Although longitudinal assessments are so far lacking, cross-sectional studies indicate that patients with refractory hypertension are at high risk of congestive heart failure, stroke, CV disease and chronic kidney disease. Underlying mechanisms of true antihypertensive treatment failure may differ from the causes of RHTN in that refractory hypertension may be neurogenic in etiology rather than being volume-overloaded, as is characteristic of RHTN. This observation is supported by the benefit of intensified diuretic therapy, including the use of a MRA for treatment of RHTN in contrast to refractory hypertension, where patients are failing all classes of treatment, including MRAs.

If the underlying cause of refractory hypertension is attributable to heightened sympathetic output, development of more effective sympatholytic therapies, including device-based approaches such as renal nerve denervation or baroreceptor stimulation, may provide an effective treatment avenue for this high-risk patient group.

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