

## Non-interventional management of resistant hypertension

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be clarified. In an effort to manage patients with resistant hypertension appropriately, clinical doctors are still racking their brains in order to find the best therapeutic algorithm and surmount the substantial difficulties in controlling this clinical entity. This review aims to shed light on the effective management of resistant hypertension and provide practical recommendations for clinicians dealing with such patients.

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**Key words:** Resistant hypertension; Antihypertensive drugs; Adherence; White coat hypertension; Secondary hypertension

**Core tip:** Patients with resistant hypertension are exposed to high cardiovascular risk and proper medical management continues to puzzle clinicians. The appropriate management of resistant hypertension is still elusive. This review provides practical recommendations for the management of resistant hypertension, aiming to help primary care physicians. It also highlights that the therapeutic scheme should always match the patient's profile in terms of safety, tolerability and effectiveness.

### Abstract

Hypertension is one of the most popular fields of research in modern medicine due to its high prevalence and its major impact on cardiovascular risk and consequently on global health. Indeed, about one third of individuals worldwide has hypertension and is under increased long-term risk of myocardial infarction, stroke or cardiovascular death. On the other hand, resistant hypertension, the "uncontrollable" part of arterial hypertension despite appropriate therapy, comprises a much greater menace since long-standing, high levels of blood pressure along with concomitant debilitating entities such as chronic kidney disease and diabetes mellitus create a prominent high cardiovascular risk milieu. However, despite the alarming consequences, resistant hypertension and its effective management still have not received proper scientific attention. Aspects like the exact prevalence and prognosis are yet to

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### INTRODUCTION

Despite impressive advances in the area of therapeutics, cardiovascular disease (CVD) continues to be the leading cause of death, even in the 21<sup>st</sup> century<sup>[1,2]</sup>. Among causative factors, hypertension carries the greatest risk for cardiovascular (CV) mortality and morbidity. With a prevalence of around 30% worldwide, individuals with high blood pressure have a five times greater risk of suffering

a debilitating stroke, whereas 50% of hypertensives will suffer from ischemic heart disease and around 7.0 million people will die each year<sup>[1,2]</sup>. Surprisingly, a considerable number of individuals with arterial hypertension remain undertreated or uncontrolled despite a combination of at least three antihypertensive drugs (including a diuretic), thus meeting the classical criteria of resistant hypertension (RH). Furthermore, since hypertension begets hypertension and hypertension worsens vascular disease and vice versa, it is reasonable to consider RH a vascular emergency. In fact, prior to the advent of pharmacological therapy, these are the patients that would progress to an accelerated and malignant hypertension phase with dire consequences.

## DEFINITION-PREVALENCE

According to the seventh report of the Joint National Committee 7 (JNC7), RH is defined as the lack of control of blood pressure (BP) or BP above the therapeutic goal despite the use of three antihypertensive drugs, including a diuretic, at optimal doses<sup>[3]</sup>. BP controlled with more than three antihypertensive medications is also included in the most recent definition of the American Heart Association (AHA)<sup>[4]</sup>. A more recent definition comes from the latest guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC). According to the authors, RH is defined as arterial hypertension above the therapeutic goal of systolic blood pressure (SBP) (140 mmHg) and diastolic blood pressure (DBP) (90 mmHg), and resistant to treatment despite the implementation of appropriate lifestyle measures and a combination therapy of three antihypertensive drugs, including a diuretic, at adequate doses<sup>[5]</sup>. With recent publicity surrounding RH, more and more studies indicate increasing frequency, but true prevalence remains largely unknown. Data from relatively small studies published so far indicate ranging prevalence from 5% in the general population to 50% in nephrology clinics<sup>[6-8]</sup>. However, more recent data from the United States and Spain suggest a prevalence of resistant hypertension of approximately 10%<sup>[9-10]</sup>. Yet, even these data are questionable due to methodological limitations<sup>[11]</sup>.

## PROGNOSIS

Similarly to prevalence, the prognosis of patients with RH remains an area widely understudied. It is well established that arterial hypertension and CV risk are a very tight dual complex and that CV morbidity and mortality is directly related to BP levels<sup>[12]</sup>. It thus seems rational to assume that patients with RH presenting with long-standing, uncontrolled, high BP might be at a much higher CV risk<sup>[13]</sup>. This assumption is further supported by the fact that most patients with RH have many other CV risk factors, such as chronic kidney disease (CKD), obstructive sleep apnea (OSA), diabetes or left ventricu-

lar hypertrophy (LVH)<sup>[4,8]</sup>. Although rationally sound, only small clinical studies and observational cohorts have tried to give a more concrete element to this relationship, demonstrating up to a six fold higher CV risk for patients with RH<sup>[14-20]</sup>. Therefore, ESH and ESC guidelines incorporated RH as a condition associated with a high risk of CV and renal events<sup>[5]</sup>.

The most significant information in this field comes from two recent studies. In a large retrospective observational study of more than 200000 patients and a median follow-up of 3.8 years, it was found that CV event rates were almost 50% higher in patients with RH compared to those without RH<sup>[21]</sup>. Although very important, this large study suffers from the inherent drawbacks of retrospective analysis of data stored in large databases. A more accurate estimation of RH-associated CV morbidity comes from a meticulous study of almost 2000 hypertensive patients with a mean follow-up of 3.9 years<sup>[22]</sup>. It was found that RH was associated with a 2.2-fold increased risk of CV morbidity compared to control patients without RH. However, the accurate risk while being uncontrolled and the exact benefit from efficiently controlling RH are yet to be found.

## MANAGEMENT

Given the relatively high prevalence of RH and the presumably high CV risk of this condition, proper management of the affected individuals should be promptly established. In general, the ideal approach of a patient with RH should focus on two goals, with the primary being identification, careful evaluation and, if possible, reversal of contributing factors, followed by an effective individualized drug regimen.

After ensuring that treatment resistance is not due to improper office BP measurement, especially in elderly patients, the astute physician has to exclude other causes of “pseudo-resistance”. The possibility of secondary hypertension should be examined, probably evaluating target-organ damage (TOD). Practical recommendations for a step-by-step approach are presented in detail.

## WHITE COAT HYPERTENSION

White coat hypertension is a commonly encountered factor that must always be ruled out. Several small studies pointed towards an increased prevalence of white coat hypertension among patients with RH<sup>[15,16,23]</sup> and a large study of more than 8000 patients with apparent RH unveiled the magnitude of the white coat effect<sup>[10]</sup>. Using ambulatory BP monitoring, it was found that only 62.5% of patients with office RH actually had true RH, while the remaining 37.5% had white coat hypertension<sup>[10]</sup>. Apart from ambulatory BP monitoring, white coat hypertension may be excluded with the use of home BP measurements as well. In a large 20 year study of more than 2300 patients with office RH, white coat hypertension was identified in approximately 30% of study participants, mainly through home BP monitoring<sup>[24]</sup>.

### Adherence to therapy

Poor adherence to prescribed medication is a major problem in the cardiovascular field. A population study of about half a million patients in Italy revealed that 33% discontinued antihypertensive drugs within 6 mo of treatment initiation and the discontinuation rate reached 50% at 5 years post-treatment<sup>[25]</sup>, with obvious detrimental consequences. Indeed, continuation of antihypertensive drugs is associated with a 37% reduction of CV events in hypertensive patients<sup>[26]</sup>. Moreover, the CV risk is 25% lower in patients with high compliance compared to those with low compliance with antihypertensive agents<sup>[26]</sup>. The problem of persistence with antihypertensive therapy in patients with RH was recently highlighted in a small study from Germany. Among 108 patients with true resistant hypertension, it was found that more than half of them were non-adherent to therapy; more impressively, among non-adherent patients, 30% were completely non-adherent and 56% were taking less than half of the prescribed drugs<sup>[27]</sup>. Although the study was small, it was well-designed and used state-of-the-art toxicological methods to assess antihypertensive drug levels, indicating that poor treatment adherence is actually exaggerated in patients with apparent RH and is a major problem. Another just published study of 339 patients with RH assessing serum levels of antihypertensive drugs confirmed the findings of the previous study since 47% of patients were non-compliant to therapy (either completely or partially)<sup>[28]</sup>.

### Clinical inertia

Clinical or physician inertia in the hypertension field can be defined as the failure of treating physicians to initiate, intensify or change therapy when BP values are above the therapeutic goal. It has long been recognized that physicians are often reluctant to appropriately manage high blood pressure levels and do not start, intensify or switch antihypertensive therapy in about one third of occasions<sup>[29,30]</sup>, reaching 50% in patients with comorbidities<sup>[31,32]</sup>. Clinical inertia seems to play a major role in RH. In a recent study of more than 3500 patients with diagnosed RH, treatment intensification (dose increase or drug addition) occurred in only 21.6% of visits with elevated BP<sup>[33]</sup>.

The observation that treatment intensification occurs in only one of five clinical visits is shocking and deserves to be examined in-depth, to be highlighted and appropriately addressed. First, it seems to reflect everyday clinical practice since the vast majority (99.5%) of clinical visits in the latter study was performed in primary care (family practice, internal medicine and obstetrics/gynecology). However, the big surprise comes from another finding of this study and regards diuretic use: instead of intensifying diuretic use by dose increment, the study reported that diuretic use was actually reduced by 15% at one year after the diagnosis of RH. Another finding of this study confirms the importance of increasing treatment intensity: treatment intensification was associated with a 64% increase in BP control at 1 year post-RH diagnosis.

### Drugs inducing hypertension

A long list of drugs (either prescribed or over-the-counter) and exogenous agents result in BP elevation and consequently either induce hypertension or contribute to resistance in drug therapy. Drug-induced hypertension is common and among the main causes of treatment resistance<sup>[34]</sup>. The most frequent agents associated with drug-induced BP elevation are without any doubt non-steroidal anti-inflammatory drugs which are widely prescribed for a variety of conditions and are also available over-the-counter<sup>[35-37]</sup>. Other common causes include oral contraceptives, hormone replacement therapy, and sympathomimetics<sup>[38-40]</sup>. Special attention needs to be drawn to drugs that are not commonly used but are essential for the treatment of specific conditions: erythropoietin for the treatment of CKD-associated anemia and myelodysplastic syndromes, cyclosporine and tacrolimus for organ transplantation, mineralocorticoids for adrenal insufficiency, glucocorticoids for a wide variety of conditions, and some newer anti-neoplastic drugs (VEGF-inhibitors and tyrosine-kinase inhibitors)<sup>[41-43]</sup>. Finally, illicit drugs and herbal supplements must not be forgotten as causes of treatment resistance in hypertensive patients<sup>[44,45]</sup>.

Some points regarding drug-induced BP elevation need to be highlighted. First is the heterogeneity of BP response to the above mentioned agents. Some patients experience excessive BP elevation while other patients exhibit little if any BP elevation. Then, the necessity of the administered drugs inducing BP elevation dictates management: (1) when the drug is not essential it can be withdrawn; (2) when the drug is essential and replacement with another less susceptible drug or dose reduction seems possible it can be tried; and (3) when the drug is essential and cannot be replaced or down-titrated then the best solution seems to be to treat the elevated BP with the more appropriate antihypertensive drugs for each condition. Last, but most important, is the identification of drug-induced BP elevation. Despite its high frequency and the easiness of its recognition, treating physicians often miss the opportunity of recognizing iatrogenic hypertension, a common identifiable cause of treatment resistance.

### Secondary hypertension

Secondary forms of hypertension are not rare and are frequently associated with treatment resistance unless the etiological factor is removed. The list for secondary hypertension is long and includes a wide variety of conditions<sup>[46]</sup>; however, a detailed presentation of these causes is outside the scope of the current review. Special attention should be given to the most common causes of secondary hypertension: primary hyperaldosteronism, renal parenchymal disease, renovascular disease and obstructive sleep apnea<sup>[34]</sup>. For example, in a large study of more than 2000 patients with RH, primary hyperaldosteronism was identified in approximately 11% of study participants<sup>[24]</sup>.

The astute physician, however, needs to know all the forms of secondary hypertension, recognize their pre-

senting symptoms, be familiar with the tests required to establish or rule out their diagnosis, and effectively treat these conditions. It has to be noted that a lot of experience is required to raise suspicion and unveil secondary forms of hypertension because there is a two-edged sword: either miss the diagnosis of a secondary form of resistant hypertension or perform several unnecessary tests without an obvious reason and with a tremendous cost. It therefore seems rational to recommend referral to a specialized center when the suspicion of a secondary form is raised by primary care physicians<sup>[5]</sup>.

### Target organ damage

The recent 2013 guidelines for the management of arterial hypertension recommend the recognition of TOD in patients with arterial hypertension<sup>[5]</sup>. The reason for this recommendation lies mainly in a more complete and accurate estimation of CV risk and the subsequent reclassification of patients with low or intermediate risk to a higher risk level, as well as the specific treatment of the various forms of TOD with appropriate antihypertensive drugs. TOD is common in patients with RH and more frequently recognized compared to patients without RH. Indeed, left ventricular hypertrophy, arterial stiffness, microalbuminuria, diastolic dysfunction and chronic kidney disease are more common in patients with RH than in control patients<sup>[47-51]</sup>. The association between RH and TOD represents a “chicken-egg” question: is it the RH that results in TOD or is hypertension more difficult to control in patients with TOD? Although available data does not allow for definite conclusions, it seems that this association is bi-directional and both types of association occur in patients with RH.

Although we do not wish to dispute the importance of identifying TOD, we believe that it is of marginal clinical significance in patients with RH. Our belief is mainly for two reasons: (1) patients with RH are already at very high CV risk, due not only to hypertension but to the frequent existence of comorbidities as well; and (2) more importantly, patients with RH are already being aggressively treated with the majority of available means of the antihypertensive therapeutic armamentarium and the recognition of TOD is not likely to alter the therapeutic regime. Therefore, the quest for TOD in patients with RH seems to be currently of little if any clinical significance.

## NON-PHARMACOLOGICAL APPROACH

Lifestyle factors (obesity, excessive salt intake, physical inactivity, smoking, increased alcohol consumption) contribute significantly to the multifactorial etiology of treatment resistance and are prominent therapeutic targets during assessment of patients with RH<sup>[4,8]</sup>. Thus, common lifestyle modifications such as dietary weight loss, salt restriction, increased physical activity, smoking cessation and moderation of alcohol intake are recommended and should be always incorporated in the therapeutic plan of individuals with RH<sup>[4,8]</sup>. However, the evidence behind

these recommendations is not always strong and often relies on potential benefits and the lack of harm.

Several lines of evidence from epidemiological longitudinal studies and randomized clinical trials indicate that hypertension is more difficult to control in obese patients and requires more antihypertensive drugs<sup>[52-55]</sup>. In a recent report from NHANES, obesity was identified as a strong and independent predictor of apparent treatment-resistant hypertension<sup>[56]</sup>. Obesity-induced treatment resistance might be mediated by sympathetic activation, volume expansion, aldosterone excess and obstructive sleep apnea<sup>[57-59]</sup>. Although the benefits of weight loss on BP are not questioned, the impact of weight reduction (through lifestyle modification, pharmacological agents or bariatric surgery) on BP in patients with RH is poorly studied and needs to be confirmed by properly designed studies. Likewise, smoking cessation and alcohol moderation have not been adequately studied in RH, despite the undisputable benefits of these changes in lifestyle factors.

The paramount importance of salt restriction in patients with RH was recently highlighted. A small, randomized, cross-over study of 12 patients with RH evaluated the effects of a low and high sodium diet on BP<sup>[60]</sup>. It was found that a low sodium diet was associated with a substantial reduction of office systolic and diastolic BP by 22.7 and 9.1 mmHg, respectively. Of major importance, a similar reduction in ambulatory BP was observed as well (20.1/9.8 mmHg), both during the day and night, despite the fact that ambulatory BP reduction tends to be significantly lower than office BP reduction<sup>[61]</sup>.

Fitness and increased exercise capacity are associated with significant morbidity and mortality benefits in patients with hypertension, prehypertension and high normal blood pressure, even in elderly patients<sup>[62-66]</sup>. The significance of regular exercise in patients with RH was recently demonstrated. A randomized study of 50 patients with RH assessed the effects of a treadmill exercise program for 8 to 12 wk<sup>[67]</sup>. It was found that regular aerobic exercise is associated with a significant reduction in ambulatory BP by 6/3 mmHg. Another small study of 16 patients with RH points towards significant benefits of heated water-based exercise<sup>[68]</sup> but further studies are needed to confirm these preliminary findings.

## DRUG TREATMENT

After all contributing factors have been carefully assessed and effectively managed, treatment of true RH, whether pharmacological or not, relies on inhibiting the pathophysiological pathways resulting in BP elevation. Activation of the renin-angiotensin system (RAS), sympathetic nervous system (SNS) overactivity and intravascular volume expansion are the three cardinal pharmacological targets in the therapeutic algorithm of an individual with RH<sup>[4,8,13,34]</sup>. The means to achieve these targets cover a broad spectrum of agents, including diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers (BBs), alpha blockers, centrally acting drugs

and other potent vasodilating agents. The most prescribed drug categories among patients with RH are RAS inhibitors (ACEi and ARBs), diuretics, CCBs and BBs. A recent report of more than 140000 patients with RH included in the large Medstat database revealed that 96.2% of patients were on RAS inhibitors, 93.2% on diuretics, 83.6% on CCBs, and 80% on BBs<sup>[69]</sup>. Chronotherapeutics might also play a role and bedtime administration of one drug or one dose might be beneficial in terms of both BP control and outcomes<sup>[70,71]</sup>; however, more solid evidence is needed before the wide generalization of this approach.

We propose a therapeutic approach of a step-by-step addition of antihypertensive drug classes in patients with RH. This approach is based on the pathophysiology of RH, the properties of antihypertensive drugs, the safety profile and the efficacy of each class of agents in RH. It has to be noted, however, that available data in RH is scarce and limited with the vast majority of antihypertensive drugs. Therefore, the proposed approach is more scientifically sound than evidence-based. Prospective studies are needed to evaluate the efficacy, safety and utility of this approach.

### Triple therapy

In general terms, combining available agents is the cornerstone of treatment of RH. The challenge, however, rests upon constructing a regime that will be both effective, in terms of blocking the majority of the implicated pathophysiological pathways, and individualized, according to the patient's profile, lifestyle, comorbidities or even financial limitations. Moreover, the optimal combination should be well tolerated by the patient, with minimal adverse events to ensure long-term adherence to therapy.

Taking into account the above considerations, a triple combination of an ACEi or ARB along with a diuretic and a CCB seems to be a reasonable regime when approaching a patient with RH for the first time. This combination is scientifically sound, widely used in everyday clinical practice, and should be applied in high doses as the first therapeutic step in patients with true RH after all forms of "pseudo-resistance" have been excluded. This combination might be applied in terms of switching previous therapy or of treatment intensification in patients already using this combination in lower doses. The proposed triple combination has several advantages in terms of efficacy, safety profile, adherence to therapy and financial costs.

In terms of efficacy, this combination seems very attractive. Inhibition of the RAS system with an ACEi or an ARB is a very useful tool to subdue high BP, especially in patients with concomitant CKD, heart failure, myocardial infarction, diabetes mellitus and most forms of TOD<sup>[5]</sup>. Combining a RAS inhibitor with a CCB or a diuretic is a very popular and scientifically sound choice, especially for black people and the elderly in whom CCBs and diuretics are of particular value<sup>[3]</sup>. Several studies have demonstrated the CV benefit of prescribing these

two combinations and, as a matter of fact, many fixed-dose combinations have been on the market for several years<sup>[72]</sup>.

In terms of safety, RAS inhibitors are known to attenuate the most common adverse events of the other two classes: peripheral edema induced by calcium antagonists and hypokalemia induced by diuretics<sup>[5,72]</sup>. In terms of persistence in therapy and cost, dual fixed combinations (RAS inhibitors plus thiazides or calcium antagonists) have been available for many years on the market and physicians are already familiar with their use. Using fixed combinations increases adherence to antihypertensive therapy<sup>[73]</sup>. Moreover, fixed combinations are usually cheaper than the administration of each drug separately and since drugs comprising these combinations are already off-patent, fixed combinations are preferred from the financial point of view. Triple fixed combinations were recently introduced in the market and are likely to improve patients' adherence to therapy with obvious health and financial benefits<sup>[74]</sup>.

In clinical practice, it is not unusual to see patients referred for RH who are actually receiving inappropriate combinations or low doses of appropriate combinations. This clinical observation provides the basis for the first step of the proposed therapeutic approach. The combination of ACEi with ARBs provides a very good example of inappropriate or non-preferred combinations. This combination was very popular during the last decade despite its moderate efficacy on BP reduction compared to other combinations, mainly due to expectations for potential benefits on target organ protection, especially cardioprotection and nephroprotection. The dual inhibition of the renin-angiotensin system suffered a lethal kick by the ONTARGET study, in which the combination did not confer any additional benefits compared to RAS monotherapy and was associated with more adverse events<sup>[75]</sup>. More recently, two other studies seem to have put the final nail in the coffin. The NEPHRON-D study found no benefit in patients with CKD<sup>[76]</sup> and the ALTITUDE study reported similar results for the combination with direct renin inhibitors<sup>[77]</sup>. Therefore, guidelines for the management of arterial hypertension strongly recommend avoiding dual RAS inhibition. Everyday clinical practice, however, is cruel. Among 140000 patients with RH included in a large database, 15.6% were treated with ACEi plus ARBs<sup>[69]</sup>.

Overall, we believe that a triple combination of RAS-inhibitors, CCBs and diuretics in high doses should be tried in all patients with true resistant hypertension before other drugs are added. Certainly, exceptions apply for this combination as well, such as patients that are intolerant of one or more drugs included in this combination, especially in high doses, since it is known that high doses of CCBs and diuretics are associated with an increased prevalence of peripheral edema and hypokalemia, respectively. Furthermore, CCBs are relatively contraindicated in patients with chronic heart failure and it is better to substitute with beta blockers. Similarly, BB should be pre-

ferred in patients with RH and symptomatic CAD.

### Thiazide diuretics

Among the antihypertensive agents available in our quiver, emphasis should be given to diuretics. This is due to the fact that volume expansion seems to be the most implicating pathophysiological cause of RH. In fact, several lines of evidence have demonstrated that over 60% of patients could gain better BP control with proper diuretic therapy. Thus, adding a diuretic, increasing the dosage of the existing one or even changing the prescribed diuretic should be the mainstay of any treatment modification<sup>[4,8,13,34]</sup>.

More specifically, hydrochlorothiazide should be used at adequate doses of up to 50 mg/d, assuming a satisfactory renal function with an estimated glomerular filtration rate (eGFR) > 40-50 mL/min per 1.73 m<sup>2</sup>. Chlorthalidone has proved to be similarly or more effective; however, it is not widely prescribed due to its limited availability in fixed dose combinations. Whenever renal insufficiency is present, as defined by levels of eGFR < 40 mL/min per 1.73 m<sup>2</sup>, loop diuretics should take their place in the therapeutic regime. Due to their relatively short duration of action, furosemide or bumetanide should be given twice or even thrice daily, whereas torsemide with its longer half-life can be given only once per day.

During the last five years, a vivid discussion has taken place regarding the comparison of hydrochlorothiazide with chlorthalidone<sup>[78,79]</sup>. Chlorthalidone is long-acting, almost twice as potent as hydrochlorothiazide at the same dose, and has a better 24 h antihypertensive profile<sup>[80,81]</sup>. In addition, chlorthalidone was used in the ALLHAT study and proved to be equal to other antihypertensive drugs<sup>[82]</sup>, while hydrochlorothiazide and bendrofluzide were used in the ACCOMPLISH and the ASCOT trials respectively and proved to be inferior to comparison therapy<sup>[83,84]</sup>. Moreover, an indirect comparison of chlorthalidone with hydrochlorothiazide in the MRFIT study pointed towards the superiority of chlorthalidone<sup>[85]</sup>. However, further studies are needed in this field and specifically in patients with RH before definite conclusions can be drawn.

### Mineralocorticoid inhibitors

Activation of the RAS and consequently aldosterone production is a very common phenomenon in RH and a principal therapeutic target<sup>[86,87]</sup>. Aldosterone excess can be efficiently blocked by mineralocorticoid receptor antagonists (spironolactone and eplerenone). Several small clinical studies during the last decade proved the efficacy of spironolactone in reducing BP in patients with RH by approximately 20/10 mmHg for systolic and diastolic BP respectively<sup>[88-93]</sup>. This unprecedented BP reduction in patients with RH seems to be independent of baseline aldosterone levels and more pronounced in specific populations such as obese people and those with obstructive sleep apnea. The beneficial effects of spironolactone were confirmed in the ASCOT study, in which spironolactone was used as fourth line therapy in 1411

patients of both treatment arms (diuretic + BBs vs ACEi + CCBs) following the addition of doxazosin (an alpha-blocker). Indeed, BP was reduced by 21.9/9.5 mmHg with spironolactone in this study<sup>[94]</sup>. Of note, patients in the first arm of the study were by definition RH as BP remained uncontrolled despite the use of 3 antihypertensive drugs, including a diuretic.

The enthusiasm for spironolactone use was somehow dampened by the findings of two recent studies. The ASPIRANT study, a double-blind, randomized, placebo-controlled study evaluated the effects of spironolactone in 117 patients with RH<sup>[95]</sup>. It was found that daytime ambulatory BP reduction with spironolactone was only 5.4/1.0 mmHg. In another, randomized, double-blind, placebo-controlled study of 119 diabetic patients with RH, the average ambulatory daytime BP reduction was 8.9/3.7 mmHg<sup>[96]</sup>.

Another significant concern regards the risk of hyperkalemia and renal function deterioration. Patients with RH are already on RAS inhibition and CKD is frequently encountered in such patients, thus increasing the risk of hyperkalemia. Therefore, extreme caution is required, especially at treatment initiation, on renal function and potassium levels. Although a specific algorithm for RH has not been yet proposed, the recommendations of AHA regarding spironolactone use in patients with heart failure seem prudent and might apply for patients with RH as well<sup>[97]</sup>. In case of gynecomastia with spironolactone, usually seen at doses above 25 mg/d, eplerenone, a more selective agent, is well tolerated and effective<sup>[98]</sup>. It has to be noted, however, that larger doses of eplerenone are usually required for the same antihypertensive effect and the significantly higher cost of eplerenone limits its use in RH.

### Other antihypertensive drugs

Treatment guidelines recommend maximizing diuretic therapy, either by using chlorthalidone or by adding mineralocorticoid antagonists or both as needed. Are these recommendations implemented in primary care? The truth in everyday clinical practice is once again cruel. Among more than 5 million hypertensive patients included in the Medstat database, 140000 were using four or more antihypertensive drugs, fulfilling the criteria of RH. The rates of chlorthalidone and mineralocorticoid antagonist use were disappointingly low: 3% for chlorthalidone and 5.9% for aldosterone antagonists<sup>[69]</sup>.

However, even in cases where chlorthalidone or spironolactone are used, a considerable proportion of individuals with RH still have uncontrolled BP. These patients will need a fifth medication with the rationale of implementing an agent with a different mechanism of action compared to the already used regime. Blockade of SNS hyperactivity could be a solution to this therapeutic dilemma. BBs are particularly effective when concomitant coronary artery disease or congestive heart failure exists. Another reasonable approach would be to combine a BB along with an alpha blocker such as doxazosin, as data has shown that it is possible to achieve a more potent an-

tihypertensive effect.

Even then, a handful of patients will still resist antihypertensive treatment, thus rendering the evaluation of the role of centrally acting antihypertensive agents (clonidine, moxonidine, methyldopa) or potent vasodilators (hydralazine, minoxidil) as the next step. Although significantly effective in lowering BP, the increased incidence of side effects, their poor tolerability and the lack of concrete data make the implementation of these agents always with caution<sup>[3]</sup>. Finally, limited data support the antihypertensive action of a non-dihydropyridine CCB complementary to a dihydropyridine one<sup>[99]</sup>; however, data is limited and requires confirmation in patients with RH.

### Failure of drug therapy

After all pathophysiological pathways have been blocked and most appropriate pharmaceutical efforts and combinations have been made, it is evident that a reasonable number of patients will still retain remarkably high levels of BP. Rendering our whole medical armamentarium ineffective or poorly tolerated, this group of patients are undoubtedly the permanent headache of clinicians working in primary care. Advanced help should be sought and these patients should be referred to a hypertension specialist as new and more efficacious treatments, mostly in the interventional sector, come into sight<sup>[100-110]</sup>.

## CONCLUSION

Whereas arterial hypertension comprises one of the most extensively studied entities in the medical literature and while a huge collection of antihypertensive agents is available in our therapeutic armamentarium, surprisingly, a considerable number of patients do not achieve optimal BP control. In fact, individuals with RH continue to be exposed to high CV risk and proper medical management continues to puzzle clinicians. In any case, a proper initial approach should include detailed evaluation, exclusion and correction of other contributing factors, along with confirmation of true resistant hypertension. Consequently, an appropriate drug regime should be sought, based on blocking the mechanisms involved in the pathophysiology of RH. At the same time, the therapeutic scheme should always match the patient's profile in terms of safety, tolerability and effectiveness. Until new drug regimens are available, newer techniques of interventional management will keep the promise to radically transform our therapeutic approach towards RH.

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