Managing resistant hypertension: focus on mineralocorticoid-receptor antagonists

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Abstract: Mineralocorticoid-receptor antagonists (MRAs) have proven to be effective in some types of hypertension, especially in resistant hypertension (RHTN). In this phenotype of hypertension, the renin–angiotensin–aldosterone pathway plays an important role, with MRAs being especially effective in reducing blood pressure. In this review, we show the relevance of aldosterone in RHTN, as well as some clinical characteristics of this condition and the main concepts involving its pathophysiology and cardiovascular damage. We analyzed the mechanisms of action and clinical effects of two current MRAs – spironolactone and eplerenone – both of which are useful in RHTN, with special attention to the former. RHTN represents a significant minority (10%–15%) of hypertension cases. However, primary-care physicians, cardiologists, nephrologists, neurologists, and geriatricians face this health problem on a daily basis. MRAs are likely one of the best pharmacological options in RHTN patients; however, they are still underused.

Keywords: resistant hypertension, aldosterone, aldosteronism, mineralocorticoid-receptor antagonists, spironolactone, eplerenone

Introduction

The association between arterial hypertension (HTN) and primary aldosteronism (PA) has been investigated for over 50 years. The first reported case was a patient with severe HTN and hypokalemia associated with elevated aldosterone secretion. In this patient, HTN was cured by adrenalectomy.[1] From this initial finding, researchers sought to establish a cause-and-effect association between HTN and elevated plasma aldosterone levels.[2] Although the PA that accompanies Conn's syndrome is well defined as a cause of secondary HTN, many aspects related to the pathophysiology, prevalence, and relevance of this association in the absence of a tumor mass detectable by conventional diagnostic methods are being discussed in research centers worldwide.[3–6] For decades, researchers have demonstrated varying degrees of association between HTN and PA,[7–14] especially the clinical presentation in normokalemia, first described in 1965.[15] Subsequently, evidence suggested an important role of aldosterone in the pathophysiological mechanism of target-organ damage observed in hypertensive disease.[16,17] Many authors have shown a relationship between aldosterone and left-ventricular hypertrophy (LVH), renal injury, vascular disease,[18–25] atrial flutter and atrial fibrillation,[26] and structural and functional alterations of medium-caliber arteries,[27,28] as well as microcirculation injuries and alterations in endothelial function.[29–35]

In 2002, Calhoun et al[36] found a PA prevalence of 20% in resistant hypertensive subjects submitted to high sodium intake (>200 mEq/24 hours) with renin dosage >12 μg/24 hours or under renin suppression (<1 ng·mL/hour). Gallay et al reported a

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PA prevalence of 17% in resistant hypertensive patients in Seattle (WA, USA) based on a high aldosterone:renin ratio (ARR).[37] Likewise, researchers from the Czech Republic showed that 19% of patients referred for treatment for moderate–severe HTN presented PA.[38] Researchers in Oslo found a prevalence of 23% of the same condition in resistant hypertensive subjects,[39] thereby confirming higher PA prevalence in individuals with resistant HTN (RHTN) than in the general hypertensive population.

In recent systematic reviews and meta-regression analyses, authors have demonstrated a wide range of prevalence in primary-care centers (3.2%–12.7%) and HTN referral centers (1%–29.8%).[40] Moreover, data on patients with RHTN in five studies reported on the relationship between PA prevalence and HTN severity. Because of the heterogeneity of PA prevalence, further multicenter studies with standardized screening and a confirmation test are necessary. On the other hand, there is no robust evidence that mineralocorticoid-receptor antagonists (MRAs) prevent more cardiovascular events in RHTN patients than other antihypertensive drugs.

In 2008, the American Heart Association defined RHTN as "... blood pressure [BP] that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts".[41] In addition, patients, who require four or more medications to control BP are considered resistant to treatment. Almost a decade later, besides the required thiazide diuretic, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and calcium-channel blockers probably constitute the "gold trio" in the treatment of RHTN.

The complex pathophysiology of RHTN involves multiple mechanisms, including hyperactivity of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, volume overload, endothelial dysfunction, and lifestyle factors. However, no specific fourth-line drug is recommended for RHTN treatment, although five antihypertensive drug classes (MRAs, α_1-adrenergic antagonists, α_2-adrenergic agonists, β-blockers, and peripheral vasodilators) are suggested as alternatives. In addition, the increased aldosterone and plasma volume in RHTN patients suggest that aldosterone antagonists should be the fourth drug for this condition. In light of the growing clinical benefits reported in RHTN, the mechanisms of action and effects of aldosterone antagonists deserve attention and are summarized herein.

Aldosterone in the cardiovascular system in RHTN
BP control

Many observational studies have linked aldosterone excess to lack of BP control in RHTN subjects. This is a clinical condition different from PA, which is a secondary cause of HTN. In RHTN, Pimenta et al[42] showed that patients with elevated 24-hour urinary aldosterone excretion presented sustained increases in 24-hour ambulatory BP, including nocturnal BP levels. Furthermore, these authors highlighted an interesting aldosterone–age interaction in relation to 24-hour systolic BP: as subjects with high ARR got older, systolic BP also increased by as much as 20 or 30 mmHg. Some authors have also indicated that a subpopulation of RHTN – uncontrolled subjects (currently referred to as refractory hypertensive patients)[43] – present increases in circulating levels of aldosterone,[44–46] which supports the relationship between aldosteronism and poor BP control. However, previous studies suggested that this association might be driven by overactivity of the sympathetic nervous system,[47,48] another common pathophysiology mechanism underlying RHTN.[49,50] Finally, a phenomenon named "aldosterone escape" was described in patients treated with ACE inhibitors or ARBs.[51,52] Aldosterone escape is a condition where after an initial decline, plasma aldosterone levels increase above those identified prior to treatment. This increase neutralizes the benefits of BP reductions and the cardiovascular and renal protection obtained with antihypertensive therapy provided by RAAS blockers,[53] which suggests a need for MRAs[54] for proper BP control.

Hypervolemia and cardiac effects

RHTN patients have concomitant intravascular volume expansion in addition to the ARR elevation, despite an extensive use of diuretics.[55] Similar findings supporting the involvement of intravascular volume expansion in the pathophysiology of RHTN have been reported by researchers at the Mayo Clinic using thoracic impedance.[56] However, increased intravascular volume is not limited to patients with measurable evidence of aldosterone excess, which suggests that other factors may contribute to fluid retention or that conventional evaluation of aldosterone levels may not accurately reflect its functional role in respect to blood volume. In fact, other important regulators, such as sympathetic outflow and plasma renin, participate in the balance of sodium and fluid in RHTN. However, aldosteronism contributes to heart-volume overload in RHTN individuals, despite the use of diuretics, leading to greater

LVH,[57–60] LV diastolic dysfunction,[52] and increased incidence of cardiovascular events,[61] including myocardial infarction, stroke, and arrhythmia.[62] Additionally, experimental studies have shown that excessive aldosterone in the presence of high salt intake in the diet induces LVH and fibrosis.[63,64]

Experimental studies and recent studies in humans[65,66] support the occurrence of clinically relevant and bidirectional interactions between aldosterone and parathyroid hormone (PTH), with potential impact on the cardiovascular system. There is evidence that PTH increases the adrenal aldosterone secretion directly and indirectly by activating the RAAS. This stimulation of PTH hormones in the RAAS may potentiate risks in the development and progression of HTN as well as increase the risk of cardiovascular disease in patients with primary hyperparathyroidism.[54,67–69]

Obstructive sleep-apnea syndrome (OSAS), autonomic dysfunction, and obesity

Goodfriend and Calhoun[70] demonstrated an association between OSAS and aldosteronism in RHTN. Several mechanisms are involved in the pathophysiology of RHTN associated with OSAS, in particular hyperactivity of the sympathetic nervous system, manifested in excitement of chemoreceptors and dysfunction of baroreceptors leading to high BP.[71] Excessive aldosterone seems to contribute to OSAS by mechanisms involving fluid retention and edema of the nasopharynx, with consequent obstruction of the upper airways.[71,72] Obesity also seems independently to stimulate the autonomic nervous system and thus contribute to the lack of BP control in RHTN individuals (Figure 1).

Aldosterone receptors, aldosterone synthase, and polymorphisms

The effects of aldosterone are mediated through its binding to MRs,[73] which promotes extracellular volume retention by a genomic pathway and endothelial dysfunction, inflammation, and oxidative stress, among other cardiovascular and renal structural and functional abnormalities by nongenomic actions.[74] In addition to this, obesity – through the release of select adipokines[75] – and overactivity of the sympathetic nervous system may stimulate aldoste-
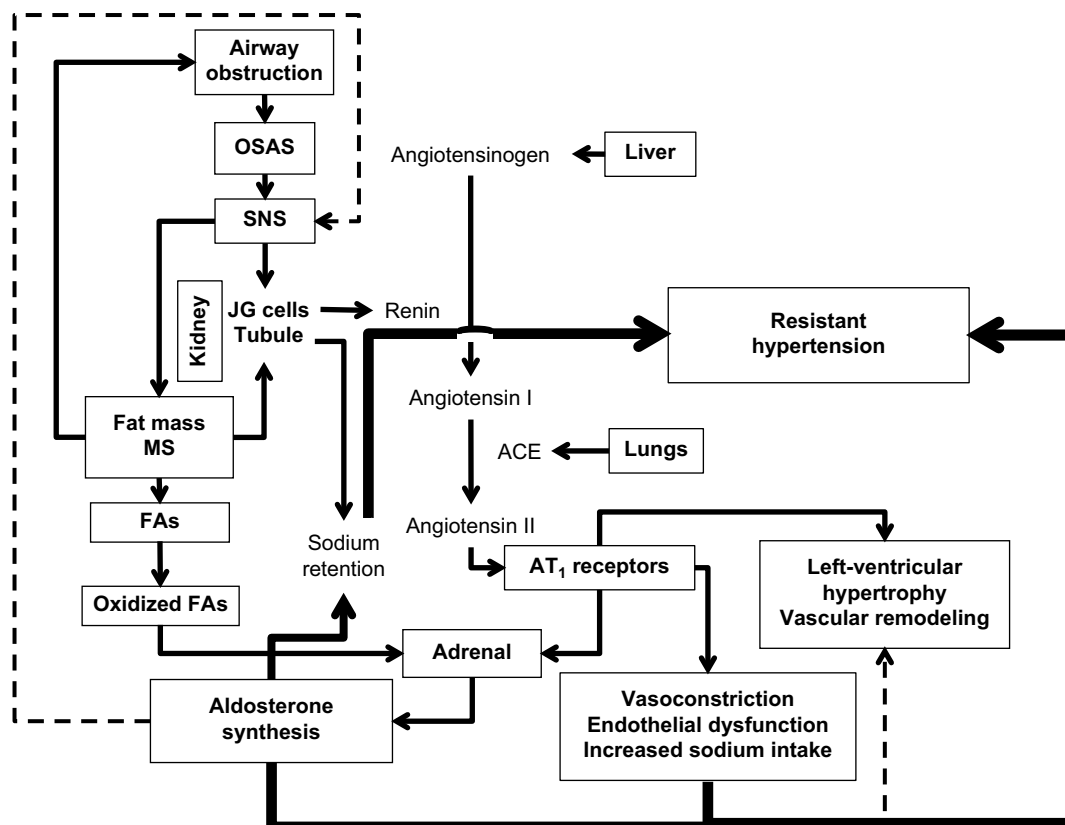

Figure 1 Relationships among factors in resistant hypertension.
Notes: Increased aldosterone secretion increases activation of the SNS. Intravascular volume control is obtained by directly influencing electrolyte balance via changes in endothelial permeability and inhibition of sodium reabsorption in proximal and distal nephrons and increased SNS activity. Solid lines indicate principal pathways; dotted lines indicate secondary pathways. Data from Goodfriend and Calhoun.[70]
Abbreviations: SNS, sympathetic nervous system; OSAS, obstructive sleep-apnea syndrome; JG, juxtaglomerular; MS, metabolic syndrome; FAs, fatty acids.

rone secretion.[70] In this context, and due to the complex condition of RHTN and its associated comorbidities, it is important to remember that aldosterone, with its elevated levels mediating several maladaptive changes, seems to be a complicating factor in subjects resistant to antihypertensive therapy.

Due to its multifactorial condition, HTN may be influenced by a genetic factor, which may also explain the current interindividual variability in plasma aldosterone levels. Aldosterone synthase (CYP11B2) is an interesting target that catalyzes the final step of aldosterone synthesis in the adrenal cortex. The differences in aldosterone biosynthesis between individuals may be attributed to genetic polymorphisms of the *CYP11B2* gene, as demonstrated by the community-based Framingham Heart Study.[76] Indeed, the –344 C/T polymorphism has been widely investigated in cardiovascular conditions. Recently, a cross-sectional study including RHTN subjects revealed that individuals with the TT polymorphism presented higher plasma aldosterone concentrations than those with the CT and CC polymorphisms, even with the use of spironolactone.[77] A meta-analysis demonstrated that homozygous individuals (CC) for this polymorphism were at 17% lower risk of HTN compared to TT subjects.[78] The presence of the T allele was also associated with higher BP[79] and urinary aldosterone excretion.[80] Furthermore, genetic polymorphisms of the MR gene (*NC3C2*) have also been explored. Ritter et al showed that subjects with RHTN carrying the G allele for the I180V polymorphism presented higher aldosterone levels, systolic ambulatory BP, and LVH, despite a higher proportion of ACE inhibitors and β-blocker use than homozygous AA individuals. Even with its cross-sectional design, this study suggests that this genetic variation might be a risk factor for resistance to antihypertensive therapy.[81]

Finally, aldosterone function has been extensively discussed in recent years as a key piece in RHTN. Therefore, the addition of MRA to the usual antihypertensive treatment in this hard-to-treat condition is of great clinical importance, since it may provide additional and pronounced BP reductions.[82,83]

Spironolactone
Pharmacological aspects
MRAs being indicated for the treatment of RHTN is based on studies that have shown effectiveness, safety, and cardiovascular and renal protection.[82,84–88] Spironolactone is an unselective MRA that has a complex metabolism and a half-life exceeding 12 hours in healthy individuals, 24 hours in patients with heart failure, and up to 58 hours in cirrhotic patients with ascites. The most common side effects observed with spironolactone – gynecomastia, breast pains, erectile dysfunction, and menstrual irregularities – result from the binding of the drug to the androgen receptor, preventing its interaction with dihydrotestosterone. The incidence of these adverse effects is not high (approximately 2%–9% of patients) and reversible after discontinuation of treatment.[82,85]

Spironolactone in RHTN
In 2003, Nishizaka et al[89] highlighted the importance of adding a low dose of spironolactone to the therapeutic scheme of patients with RHTN, with the aim of obtaining an additional reduction in BP in both black and Caucasian populations, regardless of ARR. Sartori et al[90] conducted the first prospective study involving difficult-to-control hypertensive patients with high ARR, and showed the importance of this ratio in the pathophysiology of RHTN, even in the absence of clinical manifestations, thus reinforcing the inclusion of aldosterone antagonists in the therapy of these patients. Lane et al[91] evaluated resistant hypertensive patients, adding spironolactone (25–50 mg/day) to standard triple therapy. These authors observed an additional antihypertensive effect in this group of subjects, suggesting that the addition of spironolactone may be useful, even in the absence of an elevated ARR in RHTN. Other studies[84,92–95] substantiated the importance of the addition of spironolactone in antihypertensive therapy of RHTN patients. However, the high incidence of gynecomastia and breast pain among patients taking this drug was significant.

Eplerenone
A multicenter, double-blinded, placebo-controlled trial demonstrated that eplerenone was effective in reducing BP in subjects with mild–moderate HTN compared to a placebo. In addition, no clinically relevant safety issues were observed in eplerenone-treated subjects.[96] Selective aldosterone blockade with eplerenone was also useful as an add-on therapy in hypertensive patients who were inadequately controlled on either ACE inhibitors or ARBs alone.[97] Either alone or in combination with enalapril, eplerenone also proved to be effective in regression of target-organ damage, such as LVH in hypertensive subjects[98] and albuminuria in type 2 diabetic patients,[99] but was found to be even better when combined with an ACE inhibitor. Moreover, eplerenone reduces arterial stiffness, the collagen:elastin ratio, and circulating inflammatory mediators.[100] All these findings in HTN favor the use of eplerenone as the fourth drug to treat RHTN.

The selective aldosterone antagonist eplerenone has also been explored in RHTN. This drug proved to be effective and

well tolerated, with modest changes in serum potassium in this high-risk population. At the end of a 12-week active-treatment period added to the complex medication regimen of RHTN subjects, the change from baseline in 24-hour mean BP was −12.2/−6 mmHg (P<0.0001).[82] Moreover, the addition of eplerenone enabled 39% of patients to achieve 24-hour average ambulatory BP levels <135/85 mmHg and a 63.5% success rate in achieving office systolic BP <140 mmHg. Despite this, aldosterone and renin activity could not predict BP responses to eplerenone in this study population.[82] In addition, a randomized, open-label, parallel-controlled trial demonstrated that endothelial function – assessed by flow-mediated vasodilation – improved after 12 weeks of eplerenone, which seems to be a BP-independent effect.[101] Taken together, these findings suggest that eplerenone treatment not only reduces BP levels but also limits end-organ damage.

The use of aldosterone antagonists in RHTN: current insights and perspectives

Currently, MRAs are not indicated to be used as first-, second-, or even third-line drugs in RHTN. On the other hand, due to the high prevalence of PA in RHTN, studies have shown relevant antihypertensive benefits of adding an MRA to the existing multidrug regimen.[85,102] Williams et al[83] performed the first randomized controlled trial (the PATHWAY-2 study) comparing different antihypertensive treatments in a rigorous assessment of subjects with RHTN. In this study, spironolactone (25–50 mg/day) was clearly considered the most effective drug added to the three recommended drugs – an ACE inhibitor/angiotensin II-receptor blocker, plus a calcium-channel blocker, plus a thiazide-like diuretic – in the treatment of RHTN.[49] This trial is considered a milestone, since it overcame the limitations of previous observational and interventional studies, mainly because PATHWAY-2 was designed to use active comparators (widely used antihypertensive drugs), instead of just a placebo.[103] Moreover, a recent systematic review and meta-analysis has supported it by comparing MRAs with other fourth-line antihypertensive agents in patients with RHTN. MRAs reduced BP more effectively than the other fourth-line agents in randomized and nonrandomized studies.[104]

It is well known that the effect of MRAs on BP reduction includes renal and extrarenal pathways. Treatment with MRAs has been shown to attenuate end-organ damage, mainly because of prevention of nongenomic effects of aldosterone, which lead to increased arterial stiffness and

oxidative stress. For instance, reduced cardiac hypertrophy was seen at 3- and 6-month follow-ups in RHTN subjects (with or without PA) taking spironolactone (added to the ongoing antihypertensive regimen at 25 mg/day and force-titrated to 50 mg/day at 4 weeks).[105] The BP-lowering effect and BP-independent effect contribute to place MRAs as very attractive drugs to treat the complex and multifactorial condition of RHTN (Figure 2).

The most concerning adverse effect of MRA treatment is hyperkalemia.[106,107] Therefore, periodic monitoring of serum potassium and renal function are mandatory, especially in patients at high risk of developing this disorder (elderly patients with renal impairment or diabetes).[108] Taking concurrent pharmacotherapies associated with hyperkalemia, such as potassium supplements, other potassium-sparing diuretics, and nonsteroidal anti-inflammatory drugs, should be avoided. Furthermore, the concomitant use of an MRA with ACE inhibitors or ARBs requires special attention.[109,110] Because of this, experts have recommended MRAs for subjects with RHTN only with careful monitoring of serum potassium levels. Finally, it has been demonstrated that the combined use of spironolactone with a thiazide diuretic, such as chlorthalidone, at optimal doses not only provides greater efficacy but also reduces the risk of spironolactone-induced hyperkalemia.[111]

Eplerenone in the treatment of RHTN still lacks data, but substantial efficacy and good tolerability have been demonstrated with modest changes in plasma potassium.[82] The most recently developed MRA, finerenone, has not been studied in RHTN, although its pharmacokinetic profile is promising.[112] Other agents similarly affecting aldosterone effects may be alternatives in patients with RHTN. A recent highly selective and potent aldosterone-synthase inhibitor – RO6836191 – has the potential of being used in the clinical setting.[113] Another aldosterone-synthase inhibitor – CYP11B2 (LC1699) – reduces both office and ABPM pressures in PA, but its development was discontinued because of cortisol response to adrenocorticotropic hormone stimulation was significantly suppressed in 20% of patients.[114] These findings suggest that new compounds will be identified for future use to treat RHTN.[115] Finally, thiazolidinedione agonists, which act on PPARγ receptors and are widely used in the treatment of type 2 diabetes, in addition to their known antiproliferative effects, can also suppress aldosterone production.[116] Therefore, they may potentially be useful in combination with conventional antihypertensive therapy for patients with RHTN who also have insulin resistance and type 2 diabetes.
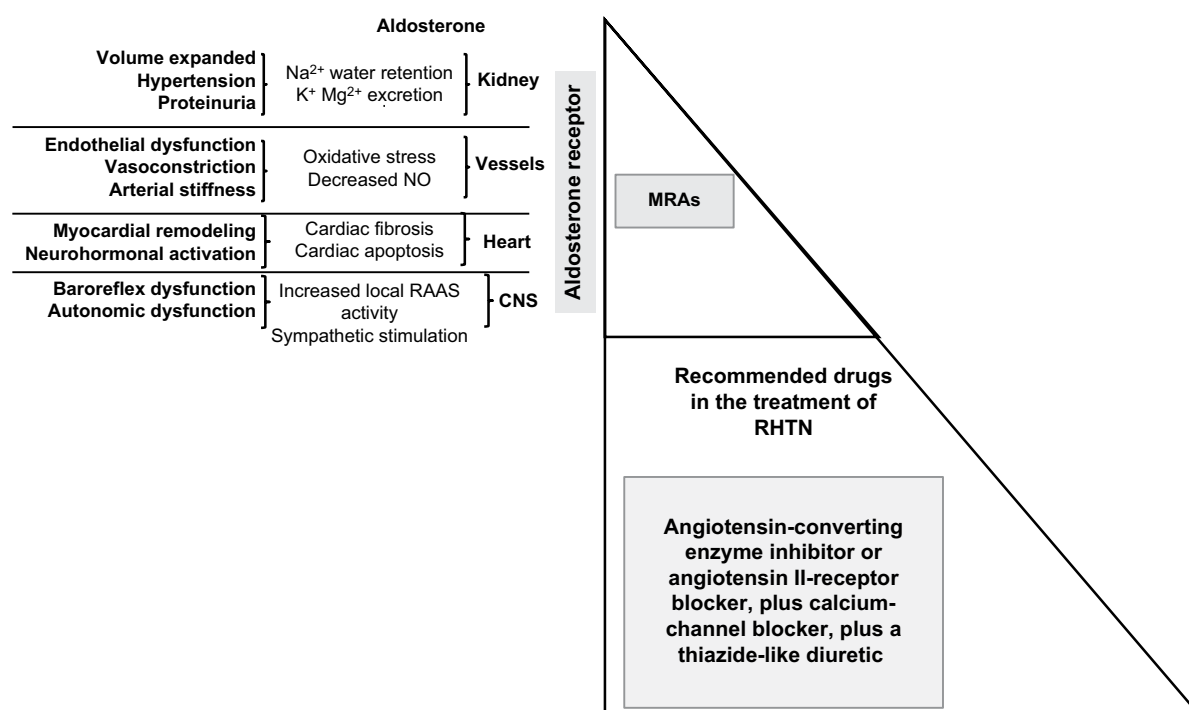
Figure 2 Fourth-line antihypertensive agents in patients with RHTN.
Notes: MRAs compete for the binding sites of aldosterone, effectively decrease blood pressure, and attenuate end-organ damage, mainly because of preventing nongenomic effects of aldosterone, which lead to arterial stiffness and increased oxidative stress.
Abbreviations: RHTN, resistant hypertension; MRAs, mineralocorticoid-receptor agonists; RAAS, renin-angiotensin-aldosterone system; CNS, central nervous system.

In conclusion, based on the many lines of evidence, such MRAs as spironolactone should be considered the fourth-line drug in the treatment of RHTN.[104,117–119] Unfortunately, a retrospective cohort study, which examined antihypertensive-medication trends from the introduction of the 2008 American Heart Association Scientific statement on RHTN to December 2014, highlighted the persistent infrequent use of recommended therapies, including spironolactone, in RHTN subjects. Spironolactone use increased by about 38% from 2008 to 2014, although with low overall prevalence: it was used in only one in ten cases of RHTN.[120] With the recent evidence, greater efforts are needed to increase the use of recommended antihypertensive drugs, including such MRAs as spironolactone, among patients with RHTN.

Disclosure

The authors report no conflicts of interest in this work.

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