Primary Aldosteronism and Drug Resistant Hypertension: A "Chicken-Egg" Story

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ABSTRACT

Drug-resistant arterial hypertension (RH) is a major risk factor for cardiovascular disease, often due to overlooked underlying causes. Identification of such causes poses significant clinical challenges. In this setting, primary aldosteronism (PA) is a frequent cause of RH and its prevalence in RH patients is likely higher than 20 %.

The pathophysiological link between PA and the development and maintenance of RH involves target organ damage and the cellular and extracellular effects of aldosterone excess that promote pro-inflammatory and pro-fibrotic changes in the kidney and vasculature.

The feasibility of adrenal vein sampling in PA patients with RH, and the clinical benefit achieved by adrenalectomy, further emphasize the need to implement systematic screening for this common form of secondary hypertension in the management of a high-risk population as RH patients.

We herein review the current knowledge of the factors that contribute to the RH phenotype with a focus on PA and discuss the issues regarding the screening for PA in this setting and the therapeutic approaches (surgical and medical) aimed at resolving RH caused by PA.

Introduction

According to recent surveys [1–3], despite the availability of several different classes of antihypertensive drugs, many patients with arterial hypertension (HT) do not reach the optimal target blood pressure (BP) for their cardiovascular risk profile. These patients are at high cardiovascular risk not only because they are exposed to uncontrolled BP values, but also because of the common concurrence of overt signs of HT-mediated organ damage (HMOD), which foretell imminent cardiovascular events. To call attention to this dreadful condition, the major scientific societies, such as the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) and the American Heart Association (AHA), have coined the term "resistant" hypertension (RH), a condition defined as BP levels above 130/80 mmHg (AHA) [4] or 140/90 mmHg (ESC/ESH) [5] despite the use of three antihypertensive drug classes, commonly including a diuretic and a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), each drug being administered at maximum, or maximally tolerated, daily doses.

Importantly, RH is not a diagnosis, but a provisional definition to be used to identify high-risk patients who deserve the utmost attention from their attending physicians. The AHA guidelines also include in this definition the subgroup known as "controlled RH," represented by those patients who achieve BP target values but require ≥ 4 antihypertensive drugs to reach this goal.

Pseudo-resistant hypertension, mostly due to the white-coat effect or absence of adherence to the therapy, must be initially excluded [4, 6, 7]; pseudo-resistant hypertension prevalence is variably reported [8, 9], but it is considered to be rather high [10]. Clinicians' inertia, in particular on inadequate drug dosage up-titration or choice of combinations, also plays a relevant role. Furthermore,

interventions on lifestyle factors such as obesity, alcohol consumption, and high sodium intake, while fundamental, are overlooked. Moreover, the lack of implementation of these measures is explicitly reported only in the ESC/ESH definition of RH.

Several conditions can result in secondary RH; common and uncommon causes are listed in ▶ **Fig. 1**. While it is difficult to establish their exact prevalence, it should be noted that in the DENERHTN study [11], when recruiting RH patients for renal denervation at French hypertension referral centers, nearly half of the 1400 selected patients were excluded due to the detection of a secondary cause. Since identifiable causes of RH are quite common, their search should be prioritized.

Large observational studies demonstrated how primary aldosteronism (PA), a condition where the adrenocortical secretion of aldosterone exceeds the amount physiologically needed to preserve body salt, water, and BP levels, is the most common cause of drug-resistant hypertension. PA is highly prevalent in the hypertensive population, ranging from 5.9 % in unselected HT patients to 11.2 % in the specialized centers setting and up to 20–30 % in the RH patients [12, 13]. The Adrenal Vein Sampling International Study-2-(AVIS-2)-RH [14], a multi-center international study that recruited consecutive PA patients submitted to adrenal vein sampling (AVS), showed that RH is a common presentation in patients seeking the surgical cure of PA. In fact, the average prevalence of RH, using the AHA 2018 definition, was 20 %, with a rate two times higher in men than in women. The rate of RH was much higher when RH was defined by the managing physicians rather than the AHA definition (50 %), which suggests that in the real-life clinical perception of resistance to achieve expected therapeutic blood pressure targets can be far more common, as compared to a structured guidelines-based AHA 2018 definition.

New genes and old factors mediating the development and maintenance of an resistant hypertension phenotype in patients with primary aldosteronism

Aldosterone is the main mineralocorticoid hormone regulating body fluid homeostasis. It acts by targeting several tissues through activation of the intracellular mineralocorticoid receptor (MR) and through non-genomic mechanisms independent from MR binding [15]. MR activation stimulates the transcription of specific genes involved in the regulation of electrolytes volume status and blood pressure in the distal nephron, as the main target, and in the vasculature, nervous system, and adipose tissues [16]. In physiological conditions, aldosterone is released by the zona glomerulosa of the adrenal glands upon regulation by several peptides, such as angiotensin II, endothelins, and urotensin 2, and K^+ levels (for rev, [17]).

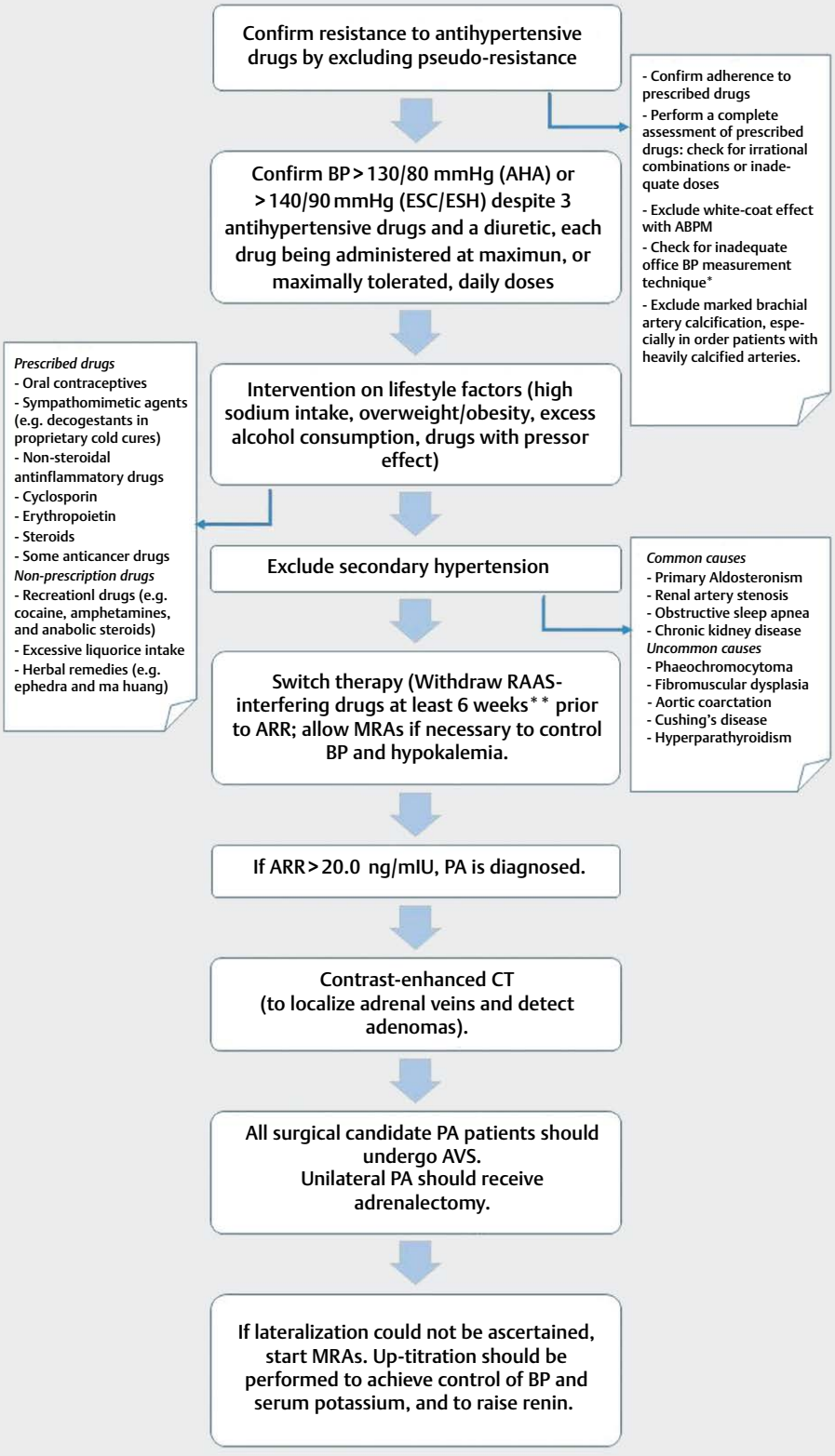
PA is a condition in which aldosterone production exceeds the amount physiologically needed to preserve body fluid homeostasis and warrant normal blood pressure. It occurs in sporadic and familial forms, the latter being associated with few germ-line mutations [18]. Many somatic mutations in genes that regulate intracellular ion concentrations (*KCNJ5* [19], *CACNA1D* [20, 21], *CACNA1H* [22, 23], *CLCN2* [24, 25], *ATP1A1*, and *ATP2B3* [26–21]) have been discovered in sporadic PA. These mutations can determine a depolarization of the adrenal zona glomerulosa cell, with ensuing autonomous production of aldosterone. The genetics of PA is now well described, with studies showing that, albeit prominent geographical variations [27], around 90 % of the aldosterone-producing adenomas (APA) carry one or more mutations in genes regulating the synthesis of aldosterone. However, the role of somatic mutations identified so far in causing the development of an APA and/or the autonomous secretion of aldosterone remains to be fully elucidated.

Recently, genome-wide association studies provided novel information on genetic loci associated with hypertension, aldosterone production, and PA [28–30]. These studies were performed by focusing on the identification, not of PA-causing genes, but of the genetic background (i. e., single nucleotide polymorphisms, SNPs) contributing to the increased susceptibility to the development of an APA or BAH. One of these studies, performed in a large, multicenter cohort of PA patients [30], showed a genetic link between PA and RH. In fact, the SNPs associated with PA development clustered near three genes (*CASZ1*, *LSP1*, and *RXFP2)* that were already associated with RH in previous studies in populations from Iceland, from the UK Biobank, and from the eMERGE and the CHARGE consortium studies [31]. The risk alleles found in *CASZ1* and *RXFP2* correlated with lower potassium levels, and the effect on potassium predicted their association with RH beyond their blood pressure effect. Moreover, by showing that over-expression of CASZ1 and RXFP2 influences adrenocortical function and modifies the basal and stimulated mineralocorticoid output in adrenocortical cells, the study provided mechanistic explanations for the previously observed association with blood pressure and RH.

The pathophysiological link between aldosterone excess and the HMOD involved in the development and maintenance of RH is well known [32]: detrimental effects of aldosterone excess are mainly due to elevated levels of oxidative stress (metabolic effect) and to inflammatory and pro-fibrotic changes (cellular and extracellular effect) in the kidney and vasculature.

From a metabolic point of view, there is a bulk of literature showing how, in a setting of inappropriate aldosterone production as in PA or in experimental models of hyperaldosteronism with a high sodium diet, the hormone promotes the generation of reactive oxidative stress (ROS) species through different mechanisms, such as the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [33] and the inhibition of the vascular expression of glucose-6-phosphate dehydrogenase [32], thereby reducing the production of NADPH and, consequently, of glutathione, one of the main defenses against oxidative damage. Aldosterone also acts on the activity of endothelial nitric oxide synthase (NOS), causing the uncoupling of the enzyme and the production of superoxide instead of nitric oxide [34].

At the vascular level, the effects of aldosterone excess are due not only to the increase of ROS and eNOS uncoupling but also to vasoconstriction [35] and wall stiffening through mechanisms modulating both the cellular components, i. e., endothelial and vascular smooth muscle cells (VSMC), and the extracellular matrix. In fact, aldosterone induces changes in the cell phenotypes by driving the endothelium to release vasoconstrictor factors such as thromboxane A2 and Endothelin1 [36] and by promoting the osteoinductive signaling of the VSMC through the MR-mediated activation of osteogenic genes such as alkaline phosphatase (ALP)



▶ **Fig. 1** Diagnostic algorithm for PA diagnosis in RH patients. Definition of RH is different in AHA and ESC/ESH guidelines. The diagnostic approach from pseudo-resistance exclusion to PA screening modified from AHA and ISH guidelines. Abbreviations: AHA, American heart association; ARR, aldosterone/renin ratio; AVS, adrenal vein sampling; BP, blood pressure; CT, computer tomography; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ISH, International Society of Hypertension; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PTH, parathormone intact molecule; RAAS, renin-angiotensin-aldosterone system; US, ultrasound.

[37]. Moreover, it inhibits AMPK signaling-dependent VSMC autophagy, which is one of the mechanisms regulating VSMC osteogenic differentiation [38].

Studies on VSMC-specific MR knockout mice [39] have shown that MR activation is essential for aldosterone-mediated vascular fibrosis because the MR upregulates pathways involved in connective tissue growth factors and metalloproteinase/metallopeptidase signaling [33]. The pro-fibrotic effect also mediates the injury in kidneys, which comprises podocyte damage and mesangial cell proliferation by the release of pro-inflammatory and pro-fibrotic factors via NFkB and Rho-kinase, as well as by EGFR-mediated PI3K-AKT and MAPK activation [40].

The main consequences of all these changes comprise vascular remodeling, i. e., an increased wall-to-lumen ratio in all resistance arterioles, including in the kidney, which is a major determinant of resistance to treatment.

Finally, although these effects of aldosterone could explain the onset of RH in PA patients, it cannot be excluded that in subgroups of PA patients who develop RH, there are subtle genetic variations or factors exacerbating the hypertensive phenotype, thus causing RH, a hypothesis that needs to be tested by future studies.

Issues in the diagnostic work-up of primary aldosteronism in drug-resistant hypertension

A continuous revision of the screening methodology for PA took place over the years, following the building up of new evidence. Plasma aldosterone concentration (PAC) measurement is known to be influenced by circadian rhythm, sodium intake, and potassium levels, and it is not unusual to find normo-aldosteronemic PA patients [41].

Renin suppression is more consistent but can lack due to the prescription of the renin-angiotensin-aldosterone system-blocker drugs. Direct measurement of active renin concentration (DRC) is faster and independent of angiotensin levels [42]. Theoretically, 24 h urinary aldosterone levels could have the advantage of overcoming PAC circadian variations and provide an integrated production of aldosterone around the clock. However, few laboratories can differentiate between free aldosterone, aldosterone-18-glucuronide, and tetra-hydroaldosterone [43–45]. Notwithstanding its dependence on the aldosterone-renin ratio (ARR) on the biochemical measure of PAC and DRC, it showed good within-patient reproducibility [46], supporting its role as a practical tool for PA screening. Considering the above-mentioned high prevalence of PA in RH, ARR is currently recommended in RH patients [4, 7], but the reported screening rate appears to be extremely low (up to 2.1 %) [47]. This is due to several reasons, the main of which being the misbelief among general practitioners, the gate-keepers of access to specialized care, that PA is extremely rare.

Another reason consists in how most antihypertensive drugs can interfere with the renin-angiotensin-aldosterone system and, therefore, ARR. For example, RH patients, by definition, undergo diuretic therapy, which, acting on volume, sodium, and potassium levels, raises renin (and to a lesser extent, aldosterone) concentration. Other commonly used drugs are ACEi/ARBs that raise renin and lower aldosterone, thus reducing the ARR and increasing false negative results and beta-blockers that lower renin levels and therefore lead to positive results [48].

When pharmacological wash-out is applied, that being the discontinuation of such drugs while switching to long-acting calcium-channel blockers and/or doxazosin, another major problem concerns BP control. On switch therapy, BP might rise to dangerous levels, possibly leading to cardiovascular events. However, according to Beeftink et al., antihypertensive drug wash-out, when performed in a well-controlled setting (such as a tertiary-level hypertension clinic), is well tolerated and does not increase the acute risk of cardiovascular events [49]. In our center, we prolong the wash-out period to 6 weeks, as we found that in many patients with PA renin is not suppressed after 4 weeks of withdrawal of RAS blockers and, conversely, it continues to be suppressed in those PA who are on beta-blockers.

As regards allowed treatment during the screening of PA, the EMIRA study showed that the MRA canrenone does not preclude an accurate diagnosis in patients with florid PA when prescribed at doses that effectively control serum potassium and BP values [50]. This indicates the usefulness and feasibility of using MRAs during the wash-out period, eventually encouraging clinicians to undertake PA screening in RH patients. In line with these findings, in a cohort of 201 medically treated PA patients with available plasma renin activity after 1 month of MRA initiation, renin levels remained suppressed (defined as < 1 µg/L per h) in exactly two third of the patients, demonstrating scarce-to-none interference on ARR [51].

After a positive ARR result, patients are commonly submitted to an exclusion test, also called a confirmatory test (oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge). The scientific evidence supporting the usefulness of these tests is very weak. In fact, two large independent meta-analyses of the studies with the more solid design concluded that they are unreliable, not adequately validated and, therefore, should not be performed [52, 53]. Moreover, these tests, which are based on the premise that aldosterone-secreting tissues in PA are autonomous from angiotensin II [54], a totally unproven hypothesis, cause special problems in patients with RH, who, by definition, are on multiple drugs interfering with angiotensin II formation or action. Furthermore, administering salt loading, either orally or IV can be dangerous in patients with left ventricular hypertrophy, a stiff ventricle, and BP poorly controlled as those with RH.

Recently, a retrospective study by Douma et al. reported a positive ARR in 20.9 % of the RH population, with a definitive PA diagnosis, a prevalence that fell to 11.3 % after applying a confirmatory test (saline loading test and fludrocortisone test) and then a test of response to spironolactone. This low estimate is, however, questionable, considering the above-mentioned limitations of confirmatory tests, the fact that ARR-interfering drugs were suspended for only 2 weeks, dietary salt intake was liberal with no data on 24h-urinary sodium excretion, and response to spironolactone "monotherapy" is not a diagnostic criterion for PA given that a good response can be seen in RH without PA [55]. Parasiliti-Caprino et al., with a prospective cross-sectional study, found a higher prevalence of PA (29.1 %) in RH patients who presented a high occurrence of HMOD (OR = 8.60 for at least one organ involved, OR 3.08 for two) [56].

These differences in reported prevalence could be due not only to study design issues. The aforementioned evidence of angiotensin II-responsiveness could be related to the phenotypic differences

between PA patients with clear renin suppression and patients with borderline-to-negative ARR, which led to replacing the concept of PA being a single entity and to propose the existence of an "aldosterone excess spectrum" [57]. Therefore, only the selection of the most "florid" PA phenotype could account for the lower prevalence reported. Moreover, if patients with borderline phenotypes are not correctly diagnosed on time, they can develop with time antihypertensive drug resistance. Lastly, aldosterone excess could be due to causes other than PA, such as obesity, menopause, and genetic polymorphisms, which contribute to resistance to antihypertensive therapy [58, 59].

Evidence of aldosterone excess, i. e. a positive ARR, as suggested in all guidelines, should be investigated with adrenal vein sampling (AVS), an interventional procedure in which the catheterization of both adrenal veins leads to the subtyping of PA in monolateral or bilateral form. AVS is technically demanding, not feasible for all patients, and not available at all centers. For these reasons, attempts were made to overcome this procedure, such as using PET-CT [60–69] or only CT-based management. The Spartacus randomized clinical trial claimed equivalence of CT and AVS-based strategy [70]. However, it should be acknowledged that the study was underpowered for its primary endpoints [71, 72]. Moreover, in the AVIS-2 Imaging study [73] 34 % of PA submitted to AVS had negative imaging and 7 % had bilateral nodules, thus raising serious concerns about an imaging-only-based strategy for identifying surgically curable PA.

Clinical data from several studies still underline the importance of this procedure, even in RH patients. In the AVIS-2-RH study, 20 % of 1450 patients with an unambiguous diagnosis of primary aldosteronism had RH, and, after adrenalectomy, hypertension was resolved in half the number of the patients [14]. Lee et al. analyzed retrospectively 48 PA patients who underwent AVS to evaluate clinical outcomes in relationship with lateralization index and contralateral suppression index: in RH patients with no clear evidence of lateralization at AVS, the rate of complete clinical success after adrenalectomy was superior in those with contralateral suppression compared with those without suppression (3 of 9 vs. 1 of 11). Considering that blood pressure was used as the outcome for clinical success, and was in fact recognized as a limitation by the authors, one must note the overall clinical success rate in 4 out of 5 RH patients with confirmed PA diagnosis even with no evidence of lateralization (with surgical or medical therapy)[74]. All the data summed up suggest clinicians to always consider searching for an underlying cause in RH patients, first and foremost PA, since adequate treatment could be then offered, possibly leading to a cure of HT, resolution of resistance, and regression of HMOD.

It should not be forgotten that other comorbidities, besides PA, cause RH, for example, severe obstructive sleep apnea (OSA). PA and OSA often coexist; mechanisms underlying this liaison are currently under study, but it is now well-known that excess of aldosterone secretion promotes fluid retention and upper airway edema [4], accounting for most of the development and the worsening of OSA and RH in these patients. Being PA highly prevalent in hypertensive patients with moderate or severe OSA [75], guidelines [4, 76] recommend performing ARR screening in these patients. In order to evaluate how much these indications are met, Conroy et al. [77] conducted a retrospective case-control study; whereas OSA patients were more likely to have PA risk factors such as RH and hypokalemia, screening for PA was underutilized. In their OSA cohort, only 8 % of eligible patients for screening were actually tested (slightly more than their control group of hypertensive patients). The coexistence of PA and OSA is largely overlooked, despite being a frequent association, especially in RH patients.

Renal artery stenosis is another potential cause of secondary hypertension. Recently, a retrospective analysis of a large cohort of PA patients to investigate the potential coexistence between PA and RAS showed that 71 of 1033 patients (6.9 %) presented both comorbidities [56]. Of them, 24 were identified as having aldosterone excess only after renal revascularization (19/24) or complete drug wash-out, meaning PA was overlooked due to the previously recognized presence of renal stenosis. Although the true prevalence of the PA-renal artery stenosis association is unknown, PA should be considered in those patients with persisting drug resistance after successful renal revascularization.

Surgical and pharmacological treatment of PA in RH

When a unilateral form of PA is demonstrated in patients with RH, adrenalectomy is the recommended therapy; as discussed below, MRAs represent the main treatment for non-surgically curable PA and also the first add-on drug recommended for RH.

Regarding surgical treatment, AVS-guided adrenalectomy still represents the best option for monolateral PA forms because it can resolve RH in almost all patients with unilateral disease [78]. In a proof-of-concept study, Torresan et al. showed the feasibility of AVS and adrenalectomy in 77 patients with PA-RH [79]; in all the 27 patients who showed a unilateral form, adrenalectomy resolved RH. Moreover, the reported outcome of biochemical cure was 96 %, and complete or partial cure of HT was 20–80 %, respectively. During the analysis of PA outcomes according to the PASO criteria [80], it should be noted that these patients often have a long history of hypertension, implying vascular remodeling and chronic arterial damage [81], often precluding complete clinical recovery. The above-mentioned AVIS2-RH study [14], in which AVS-guided adrenalectomy resolved BP resistance to antihypertensive treatment in all patients, confirmed that surgical treatment of unilateral PA represents the optimal management of PA patients with RH.

Recent studies offered new insights linking pharmacological aldosterone blockade, PA, and RH. The PATHWAY-2 [82] study and sub-studies showed that spironolactone is effective as an add-on therapy in RH treatment regardless of whether PA concurs, with significant results on blood pressure and thoracic volume reduction. Data from the RENALDO study [83] revealed how responsiveness to spironolactone is not predicted by aldosterone levels, as the main action is thought to be directed at counteracting sodium retention and chronic volume expansion [81], probably the two most important factors in the development of RH. To better understand experimentally how MRAs act independently on aldosterone action, Maeoka et al. compared the epithelial sodium channel (ENaC) activity in mice lacking aldosterone and in mice lacking the MR receptor. They showed how ENaC activity is maintained along a substantial portion of the aldosterone-sensitive distal nephron even when aldosterone is absent, thus indicating how other hormones beside aldosterone (such as cortisol) may maintain renal MR activity and therefore explaining part of MRAs action [84].

While most clinical studies in RH patients were conducted with spironolactone, other MRAs currently used in several clinical conditions (from heart failure to chronic kidney disease with concomitant type 2 diabetes) deserve attention. Pharmacological differences in these agents bring the possibility of a more tailored therapy in PA/RH patients.

Spironolactone is a steroid-based MRA recommended as the fourth drug in RH patients by ESH and ESC guidelines [4, 7]. Other than previously reported results, long-term effects in RH non-PA patients are reduction in left ventricular mass [85, 86], albuminuria, and echocardiographic parameters of hypertensive heart disease, thus demonstrating improvement in HMOD [87]. Another recent study [88] showed an improvement in aortic properties (ascending aorta pulsatility, distensibility, and pulse wave velocity) independent of blood pressure levels, supporting the hypothesis of direct effects of aldosterone on the arterial wall, such as promoting fibrosis; notably, in this study, 60 % of the patients were diagnosed with PA and 66.7 % had OSA.

Eplerenone, the second-generation steroid-based MRA, due to a more selective aldosterone binding, holds the advantage of having minimal sexual and metabolic side effects. ESC/ESH 2018 guidelines suggest its use in RH as an alternative to spironolactone in case of side effects.

In the last years, two non-steroidal MRAs: esaxerenone and finerenone, with even higher selectivity and binding affinity on MR were developed. While the former has only been approved in Japan for the treatment of essential hypertension [89], the latter was approved in 2021 by FDA with the indication for cardio-renal protection in adults with CKD associated with type 2 diabetes. In addition to a significant reduction in eGFR decline and entity of albuminuria, FIDELIO-DKD and FIGARO-DKD studies [90, 91] showed a lower frequency of hyperkalemia; considering the high prevalence of CKD and hyperfiltration with albuminuria in PA and considering the recent results obtained with MRA on RH, it could be hypothesized a possible role for finerenone in these settings.

A recently developed drug class is represented by the direct aldosterone-synthase inhibitors. A phase 2 of a multicentre, randomized, double-blind, placebo-controlled trial with baxdrostat for treatment of RH recently showed a significative reduction in BP associated with a clear decrease in plasma aldosterone level and a (compensatory) increase in plasma renin activity, without any effect on cortisol levels. Systolic blood pressure declines of 20.3 mmHg, 17.5 mmHg, 12.1 mm Hg, and 9.4 mmHg were respectively reported in the 2 mg, 1 mg, 0.5 mg, and placebo groups [92]. A low rate of adverse events was reported, and discontinuation was not related to them. About a possible specific role in PA patients (either with or without RH), one registered study is currently recruiting (ClinicalTrials.gov Identifier: NCT04605549).

Among other new therapies, Schlaich et al. evaluated the role of a dual endothelin antagonist, aprocitentan, on BP in patients with RH who were not submitted to a full work-up for PA [93]. Endogenous ET-1 can contribute to maintaining high BP values and aldosterone secretion in both PA and RH patients and endothelin receptor blockade lowers plasma aldosterone levels via different mechanisms in primary aldosteronism and in high-to-normal renin hypertension [94]. Thus, it could be interesting to investigate the possible role of aprocitentan in counteracting aldosterone excess in PA/RH patients.

Lastly, along the recent wave of new interest in renal denervation in RH patients, scant data are available about patients with aldosterone excess, mostly because secondary cause of hypertension represents an exclusion criterion. In one trial, Liu et al. [95] compared adrenalectomy plus renal denervation applied to the adventitia of the renal artery with adrenalectomy alone in PA patients with RH; a more significant reduction in BP in the first group (42.2 ± 21.6 mmHg vs. 29.8 ± 13.5 mmHg, p = 0.029 between the groups) along with an overall good safety profile were claimed, although doubts remain on the rationale and utility of the procedure considering the proven efficacy of adrenalectomy itself [96, 97].

Conclusions

RH is often due to underlying causes, whose identification represents a challenge because of the presence of interfering treatment. Screening of secondary causes in RH patients is underused, even though recommended by all major guidelines. Moreover, available data highlight the feasibility of AVS and the excellent clinical results achieved by adrenalectomy in PA/RH patients [79]. Altogether data suggest implementing screening and treatment for secondary hypertension to identify aldosterone excess also in the presence of OSA or RAS. Regardless of the presence of PA, MRAs and aldosterone-synthase inhibitors could be game changers in RH treatment owing to their multiple benefits, counteracting the multiple effects of aldosterone excess on various organs such as the heart, kidney, and blood vessels. Data are awaited from new drugs such as non-steroidal MRAs and aldosterone-synthase inhibitors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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