REVIEW ARTICLE

Primary aldosteronism 2.0: an update for clinicians on diagnosis and treatment

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ABSTRACT

Primary aldosteronism (PA), characterized by inappropriately high concentrations of the adrenal-derived hormone aldosterone, is the most common endocrine cause of arterial hypertension. As compared with individuals with essential hypertension, patients with PA have a significantly increased cardiovascular risk that cannot be fully reversed by common antihypertensive treatment because of blood pressure–independent deleterious effects of aldosterone. Measurement of the aldosterone to renin ratio (ARR), reflecting the degree of aldosterone excess, is the classic screening test for PA, but thresholds for an elevated ARR vary substantially and are arbitrary, as there exists a wide disease continuum that spans from preclinical stages to overt PA. Treatment approaches for PA with either mineralocorticoid receptor antagonists for bilateral disease or unilateral adrenalectomy for aldosterone-producing adenomas (APA) are highly effective to mitigate the excess cardiovascular risk associated with PA. Subtype classification according to the dichotomous concept of unilateral PA, mainly due to APAs, vs bilateral PA, mainly due to bilateral adrenal hyperplasia, has been recently challenged by advances in the pathophysiologic understanding and therapeutic spectrum of PA. The implementation of current PA guidelines into clinical routine is extremely poor, as reflected by the fact that most patients suffering from PA remain undiagnosed and probably untreated. Pragmatic approaches are required to address this public health problem. In this review, we present an up-to-date overview on the clinical significance, diagnosis, and treatment of PA, with the aim to provide guidance for clinicians regarding the management of this disease, paying particular attention to its feasible implementation into daily clinical routine.

Introduction Given that elevated blood pressure (BP) is the leading global contributor to premature death, efforts to improve the diagnosis and treatment of arterial hypertension should be a public health priority.[1-3] Most patients with arterial hypertension are classified as having essential hypertension, with no specific but rather a variety of different causes. However, it is estimated that a few percent of hypertensive patients suffer from primary aldosteronism (PA), with increasing prevalence according to the degree of arterial hypertension.[4] PA is a secondary endocrine form of arterial hypertension that is characterized by inappropriately high plasma aldosterone concentrations (PACs) derived from 1 or both adrenal glands.[5] The excessively high cardiovascular risk in patients with PA vs those with essential hypertension underscores the importance of case detection and adequate treatment of this disease.[6] Although targeted treatment of PA is highly effective, epidemiologic data suggest that the vast majority (probably >99%) of PA patients worldwide remain undiagnosed and probably untreated, thus contributing to an unnecessary high public health burden.[3] The largely missing implementation of guidelines for the diagnosis and treatment of PA into daily routine care is of concern, requiring a thorough evaluation of the underlying causes for this problem and approaches on how to overcome it.[7] To address this issue and to provide an up-to-date overview on relevant aspects regarding PA, including a pragmatic guidance for clinicians on the diagnosis and treatment of this disease, we drafted this narrative review. After a brief introduction on the pathophysiology, definition, and forms of PA, we describe the clinical

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symptoms and significance of PA before outlining the respective screening and confirmatory tests. Then, we summarize the approaches to the differential diagnosis of the subtypes of PA and provide guidance regarding the therapy of this disease. Finally, we discuss the public health perspective of PA.

Pathophysiology of primary aldosteronism From an evolutionary perspective, the mineralocorticoid receptor (MR) that mainly mediates aldosterone effects was required to live in environments where salt (sodium) is scarce (eg, after moving from the sea to land), as its main function is to retain sodium and subsequently also water, while promoting potassium excretion, thus allowing for consumption of, for example, potassium-rich meat and plants.[8,9] There was obviously an evolutionary advantage for individuals with a genetically upregulated renin-angiotensin-aldosterone system (RAAS) as, for example, Yanomama Indians from the jungles of southern Venezuela and northern Brazil, who live in an almost salt-free environment, have a highly activated RAAS but normal to low BP.[10] By contrast, African Americans usually follow a high-salt diet and suffer from exceptionally high rates of arterial hypertension and cardiovascular diseases that may be a consequence of their high sensitivity to salt.[11] It has been hypothesized (despite many controversies) that the slave trade from Africa to America, with volume depletion due to limited water access and diarrheal disease, might have contributed to a survival advantage of individuals with good sodium reabsorption.[11] It is thus crucial to understand that an evolutionarily upregulated RAAS and a salt-rich Western diet work in concert to exert adverse cardiovascular effects, while an activated RAAS as in the Yanomama Indians can be a beneficial and healthy physiologic adaptation to the respective environmental conditions.

Regarding the physiology of the RAAS, we refer the reader to other excellent reviews.[8,12-14] In brief, aldosterone mediates its effects via MR-dependent and MR-independent pathways. The main MR-mediated classic effect of aldosterone is to increase the expression of the epithelial sodium channel (ENaC) of the principal cells of the collecting tubules of the kidneys, which increases sodium reabsorption and in turn leads to potassium (K^+) and hydrogen (H^+) excretion. Consequently, aldosterone causes extracellular fluid volume expansion and BP increase. Aldosterone binds also to MR expressed in various extrarenal tissues, thereby exerting several pleiotropic effects, for example, in the cardiovascular or nervous system and adipose tissue.[12] Of note, cortisol has a similar affinity to MR as aldosterone and circulates at nearly 1000-fold higher concentrations, but expression of 11β-hydroxysteroid dehydrogenase type 2 in aldosterone target cells inactivates cortisol to cortisone (of note, licorice can also inhibit this enzyme, thus potentially causing a PA-like phenotype).[14]

Regulation of aldosterone secretion from the zona glomerulosa of the adrenal cortex is far more complex than our original concept of the RAAS, as several factors participate in this process, including mainly angiotensin II (ie, the most important stimulus) and potassium, but also adrenocorticotropic hormone, endothelins, urotensin 2, gonadotropin-releasing hormone (potentially due to aberrant hormone receptor expression), and others.[9,15,16] It is imperative for clinicians to understand that a strong stimulus for renin secretion (eg, by reduced renal perfusion / pressure, low NaCl, or high sympathetic tone) stimulates aldosterone secretion due to angiotensin II. Thus, laboratory results showing elevated aldosterone (even if extremely high) and renin concentrations just reflect a physiologically stimulated endocrine system but are no indication of PA, which can be ruled out in such cases. In general, our understanding of aldosterone regulation has also considerably improved thanks to the discovery that more than 90% of aldosterone-producing adenomas (APAs) carry somatic mutations that increase aldosterone secretion, mainly due to enhanced calcium influx, as reviewed elsewhere.[17,18] In brief, these mutations are in the K^+ channel Kir3.4 (*KCNJ5*), Ca^{2+} channel $Ca_V1.3$ (*CACNA1D*), α-1 subunit of Na^+/K^+ ATPase (*ATP1A1*), plasma membrane Ca^{2+} transporting ATPase 3 (*ATP2B3*), Ca^{2+} channel $Ca_V3.2$ (*CACNA1H*), Cl^- channel ClC-2 (*CLCN2*), β-catenin (*CTNNB1*), and / or G-protein subunits αq/11 (*GNAQ/11*).[17] Based on this concept of PA as a largely genetic disorder, it has been hypothesized that there is an age-dependent accumulation of these somatic mutations contributing to a continuum between mutations in single cells, (micro)nodule formation, and eventually APA development.[17] As these processes may occur in parallel in both adrenal glands and at different disease stages (as documented in histopathologic studies), it appears rather arbitrary to make certain cutoffs for PA diagnosis, and it also questions the clear distinction between unilateral and bilateral disease.[17] Apart from the above-described somatic mutations that increase aldosterone secretion, there are various other mechanisms, such as other driver mutations of tumorigenesis, epigenetics, and microRNAs, which alter the balance between adrenal cell death and proliferation to favor APA development.[18] The genetic diversity of PA cases may give rise to a tailored personalized management and treatment of this disease in the future.[19]

Definition and forms of primary aldosteronism Although PA due to APA is historically known as Conn syndrome, named after Jerome W. Conn, who described a PA case in 1955, it was actually Michał Lityński, a Polish internist, who was the first to describe 2 cases of PA even 2 years earlier, in 1953.[20,21] Lityński concluded his 2 case reports with the notion that arterial hypertension in these patients was due to adrenocortical

tumors with overproduction of mineralocorticoids, but it took many years before his discovery of PA was appreciated in the international scientific literature by a letter published in *The Lancet* in 1991.[20,21]

According to the Endocrine Society guideline,[5] PA is currently defined as a group of disorders in which aldosterone production is inappropriately high for the sodium status, relatively autonomous of the major regulators of secretion (angiotensin II, plasma potassium concentration), and nonsuppressible by sodium loading.[5,9]

Prevalence estimates for PA in patients with arterial hypertension vary considerably due to heterogeneity in testing, arbitrary threshold, and selection bias, but it can be assumed that roughly 5% to 15% (or even more) of the general hypertensive population suffer from PA.[22-25] It is imperative to appreciate that there is a broad continuum of inappropriate aldosterone production covering a wide spectrum of the disease stages, from subclinical stages to overt PA, so that a binary classification with a clear discrimination between the presence and absence of PA is somewhat arbitrary.[24] Of note, even normotensive individuals can suffer from PA or some sort of aldosterone excess, initially reflected by suppressed renin, indicating future risk of developing arterial hypertension and cardiovascular disease.[24]

In general, we differentiate between sporadic forms of PA and the relatively uncommon (<5%) familial forms, termed familial hyperaldosteronism type 1 to 4, which are caused by different germline mutations and typically manifest as an early-onset PA (usually in childhood).[17] Therefore, it was suggested that genetic testing should be reserved for patients with early-onset PA (ie, <20 years of age), irrespective of the severity of the clinical phenotype, and for patients with a family history of PA.[26] In the diagnostic workup, clinicians should aim to differentiate between unilateral (mainly due to APA) and bilateral forms (historically ascribed to bilateral adrenal hyperplasia) of PA, as this significantly dictates the further treatment approaches. Unilateral forms of PA that are present in roughly one-third of all PA cases are potential candidates for surgery, that is, unilateral adrenalectomy, whereas bilateral forms are treated with pharmacotherapy. The nowadays routinely recommended histopathologic classification of surgically treated PA by CYP11B2 immunohistochemistry (ie, antibodies against aldosterone synthase) to identify the sources of aldosterone secretion was the basis for the new nomenclature and definition of adrenal histopathologic features.[27,28] In detail, the new classification system includes APA, aldosterone-producing nodule, aldosterone-producing micronodule (formerly termed "aldosterone-producing cell cluster"), aldosterone-producing diffuse hyperplasia, and (extremely rare) aldosterone-producing adrenocortical carcinoma.[27,28]

Clinical symptoms and significance of primary aldosteronism There is no specific and reliable clinical phenotype of PA, but clinicians should be aware that the prevalence of PA increases with the severity of arterial hypertension (particularly in resistant hypertension), and the disease is usually diagnosed between the age of 20 and 60 years (mean age at diagnosis is roughly 50 years).[23,29,30] Although hypokalemia is typically present in severe forms of PA, it is definitely not a condition sine qua non, as the majority of patients with PA have normal serum potassium levels (in particular those with milder and bilateral forms of PA).[22]

In PA, increased sodium reabsorption is paralleled by water reabsorption, thus usually preventing hypernatremia at the cost of hypervolemia, which in turn promotes hyperfiltration in the kidneys. Therefore, PA patients often yield high glomerular filtration rates and frequently suffer from various degrees of albuminuria.[31] Hypervolemia and hyperfiltration may also stimulate natriuretic peptides and cause polyuria in these patients.[31] Individuals with PA were also shown to have a reduced salt (NaCl) taste perception; thus, they consume more salt than patients with essential hypertension.[32] Metabolic alkalosis is also a classic biochemical feature of severe forms of PA. Interestingly, patients with PA were shown to have altered calcium metabolism with increased calcium excretion in urine and feces, which in turn stimulates parathyroid hormone secretion and may lead to secondary hyperparathyroidism.[33]

As compared with individuals with essential hypertension, patients with PA are at a significantly increased cardiovascular risk, even at the same BP levels.[6,34] A systematic review and meta-analysis showed that in PA patients vs essential hypertensive patients there was an increased risk of stroke (odds ratio [OR], 2.58; 95% CI, 1.93–3.45), coronary artery disease (OR, 1.77; 95% CI, 1.10–2.83), atrial fibrillation (OR, 3.52; 95% CI, 2.06–5.99), and heart failure (OR, 2.05; 95% CI, 1.11–3.78), with similar results for unilateral and bilateral forms.[6] PA also confers an increased risk of various other pathologies, such as renal and metabolic diseases, and is associated with reduced quality of life.[14,35-37] The excessively high cardiovascular risk in PA patients, which can be effectively lowered by targeted treatment of the disease, underscores the importance of timely diagnosis and treatment.[37-40] Clinicians must be aware that even when BP is adequately controlled by first-line antihypertensive medications in their patients, this does not adequately mitigate the adverse consequences of aldosterone excess if these patients suffer from unrecognized PA, as there is a variety of BP-independent adverse effects of MR activation that include, among others, proinflammatory, prothrombotic, proatherosclerotic, and metabolic effects.[12,31]

Screening test for primary aldosteronism The recommended screening test for PA is based on the determination of ARR, as it reflects the degree of aldosterone synthesis that is autonomous

TABLE 1 Selection of clinically relevant factors influencing the aldosterone to renin ratio

Factors that can decrease the ARR and potentially cause false-negative results of the ARR test (main pathophysiologic mechanism)
Diuretics (renin increase due to reduced extracellular fluid and sympathetic activation)
ACEIs and ARBs (compensatory renin increase due to blocking of the renin--angiotensin-aldosterone system)
Hypokalemia (suppression of aldosterone secretion)
Dietary sodium restriction (compensatory renin increase)
Recumbency (decrease in aldosterone level)
Factors that can increase the ARR and potentially cause false-positive results of the ARR test (main pathophysiologic mechanism)
β-Blockers (renin suppression)
ARR measurement in premenopausal women in the luteal phase of the menstrual cycle (increase in aldosterone due to antimineralocorticoid effect of progesterone)[a]
Hormonal contraceptives (increased angiotensinogen production in the liver with subsequent decrease in renin levels)
Nonsteroidal anti-inflammatory drugs (possible decrease in renin level due to increased sodium and water reabsorption)
Aging (lower renin level)
Chronic kidney disease (lower renin level)

a Only if renin is determined as direct renin concentration

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARR, aldosterone to renin ratio

with reference to its principal stimulus, renin.[5,14,29,31,41,42] Blood collections for determination of PAC and renin (measured either as direct renin concentration or plasma renin activity) should be preferentially performed in a usual ambulatory setting (in the morning and in a seated position) on liberal sodium intake and in a potassium-replete state.[5,22] Several factors including, for example, medications, posture, or serum potassium, can affect aldosterone, renin, and ARR (TABLE 1), and there is also significant variability with respect to assay methods and thresholds.[5,43-48] Therefore, a single normal or low PAC or ARR should not always completely exclude PA, and repeated measurements may be considered (at best with optimized sampling conditions) in dubious cases with high clinical suspicion, in order not to overlook the disease.

Ideal conditions for PA screening, as it is still performed in several expert centers, would therefore require discontinuation of all antihypertensive drugs (eg, for 2 weeks) or at least those with a strong impact on the RAAS and, depending on the clinical situation, replacing them by drugs with minimal interference, such as nondihydropyridine calcium channel blockers, α1-adrenergic antagonists (eg, prazosin or doxazosin), moxonidine, or dihydralazine.[5,22,49,50] Such an approach is, however, "impractical and infrequently necessary" as noted by Vaidya et al,[51] and current guidelines suggest that screening for PA under ongoing antihypertensive medications is feasible, even when the patient is using, for example, MR antagonists (MRAs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or β-blockers (of note, ARR should preferably be measured before the intake of the morning dose of the medication).[5,42,51,52] Moreover, clinical decision can be made in accordance with the expected effects of these drugs on the RAAS, as detailed elsewhere.[50] A rough practical guidance for clinicians could be that clear positive or negative ARRs under ongoing antihypertensive medications should be accepted as such. In the case of an ARR close to the respective cutoff, a repeated measurement should be considered if the clinician is unsure about the diagnosis and / or RAAS-interfering medications or conditions (TABLE 1) suggest that a repeated measurement may significantly alter the test result. For example, a negative ARR despite β-blocker therapy may be even more clearly negative without this medication, so there is no need for a repeated measurement, whereas in the case of a negative ARR close to the cutoff on ACEI or ARB therapy, a repeated ARR measurement (eg, in 2–3 weeks) should be considered, ideally after medication washout, as the test may turn out positive. If this approach is too complicated and not feasible, the default option should always be to measure the ARR if this is indicated, and to proceed with the result regardless of interfering medications and conditions, rather than to not measure the ARR at all.

It is officially recommended to screen for PA in hypertensive patients at a high risk of this disease (TABLE 2), but given the prevalence and public health significance of PA, several experts advocate for a general screening, and thus for measuring the ARR in all hypertensive patients.[5,22,51] Measuring the ARR in new-onset hypertension, as suggested by some experts, would usually enable to obtain laboratory measurements without the potential impact of RAAS-interfering medications, an approach that has already led to good clinical outcomes.[53] Importantly, the general screening of all hypertensive patients for PA has been shown to be cost-effective.[54,55]

The classic concept of dealing with this screening test is that an ARR above the respective laboratory- and center-based thresholds indicates a positive (ie, pathologic) screening test, provided that PAC is also above a certain level (eg, >5–10 ng/dl) (commonly used ARR cutoff values are shown in TABLE 3).[51] When interpreting the results of the aldosterone and renin measurements and the consequent ARR, it is crucial to understand that the ARR is significantly denominator-, that is, renin-dependent. As a suppressed or low renin level is (with few exceptions) present in all PA patients, paying attention to the renin level, rather than the PAC, should be the first step in interpreting this screening test.[51]

Detailed measurements of several components of the RAAS (of note, several angiotensins can be determined), referred to as RAS-Fingerprint, may also be useful for the diagnosis of PA and further treatment guidance, along with detailed steroid profiling, other steroids (eg, marinobufagenin),

TABLE 2 Candidates for screening for primary aldosteronism

Characteristics of patients who should be screened for primary aldosteronism according to the Endocrine Society
Resistant hypertension (ie, hypertension despite treatment with 3 different antihypertensive drugs)
Sustained blood pressure of 150/100 mm Hg
Controlled blood pressure on 4 or more antihypertensive drugs
Arterial hypertension and hypokalemia
Arterial hypertension and adrenal incidentaloma
Arterial hypertension and sleep apnea
Arterial hypertension and family history of early-onset arterial hypertension or stroke (<40 years)
Hypertensive first-degree relatives of patients with PA
Debated expansion of populations to be screened for primary aldosteronism
Arterial hypertension and atrial fibrillation
New-onset arterial hypertension
All patients with arterial hypertension

TABLE 3 Commonly used cutoff values for the aldosterone to renin ratio (adapted from the Endocrine Society[5])

Aldosterone	PRA, ng/ml/h	DRC, mU/l	DRC, ng/l
PAC, ng/dl	20	2.4	3.8
	30	3.7	5.7
	40	4.9	7.7
PAC, pmol/l	750	91	144
	1000	122	192

Abbreviations: DRC, direct renin concentration; PRA, plasma renin activity, PAC, plasma aldosterone concentration

as well as machine learning and artificial intelligence tools, which are, however, beyond the scope of this review.[56-59]

Confirmatory tests for primary aldosteronism Patients with an elevated ARR along with suppressed renin and a PAC greater than 20 ng/dl plus spontaneous hypokalemia can be diagnosed as having PA.[5] For all other patients with a positive screening test, it is officially recommended to perform confirmatory tests in order to confirm or exclude PA.[5] In detail, there are 4 classically used confirmatory tests, namely, the saline infusion test, oral salt loading test, fludrocortisone suppression test, and captopril challenge test, as reviewed elsewhere.[5,60] These tests are based on the concept that in PA, aldosterone levels are not suppressible by, for example, intravenous sodium loading or other interventions. Although current PA guidelines recommend these confirmatory tests, systematic reviews and meta-analyses concluded that they are based on very low-quality evidence, and in most scenarios their use resulted in an excess of missed cases.[60,61] Moreover, their added value is minimal when there is already a high pretest probability of PA.[60,61] Therefore, the systematic use of these confirmatory tests in clinical practice seems not to be justified by available evidence. It could be considered to bypass these confirmatory tests and proceed with further management based only on the ARR test results and the clinical characteristics of the respective patient. With reference to this, it has been proposed that patients at a high risk for PA and with a positive ARR test result should be considered to have PA unless proven otherwise, whereas PA is very unlikely in patients with a normal ARR and low PAC.[51]

Subtype classification of primary aldosteronism Subtype classification of PA is required to differentiate unilateral, and thus potentially surgically curable, forms of PA from bilateral forms that are generally treated with medications. As outlined above, there seems to be a continuum from normal RAAS to relative and absolute aldosterone excess, with APA being the tip of the iceberg, but bilateral and milder forms of PA are the most common disease types.[14,62]

The first step in the differential diagnosis of PA is to perform an abdominal computed tomography (CT) scan (or magnetic resonance imaging in young patients) in order to exclude adrenocortical carcinoma as a very rare cause of PA.[5] The size of APA is in most cases 1 cm (or slightly smaller) to less than 2 cm (of note, in patients with PA, adrenal tumors with a size >3–4 cm are thus unlikely to be APA).[63] Importantly, CT scans do not provide any information on the potential endocrine function of the detected adrenal lesions. Furthermore, due to increasing prevalence of nonfunctioning (ie, hormonally inactive) adrenal incidentalomas with age, adrenal venous sampling (AVS) remains the gold standard to differentiate unilateral forms of PA, when surgery is desired, from bilateral ones. AVS is based on the concept of measuring PAC in the adrenal veins, and should be pursued in most surgical candidates, the only exception being young patients with spontaneous hypokalemia, marked aldosterone excess, and a unilateral adrenal mass on CT, who can proceed directly to unilateral adrenalectomy.[5] The traditional cutoff for younger age is below 35 years, but according to a recent international retrospective study,[64] imaging allowed correct identification of the responsible adrenal gland in all patients under 45 years with hypokalemia and a unilateral adrenal nodule.[64]

The only randomized trial in this field, the SPARTACUS trial (Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scans)[65,66] has, however, challenged the view on AVS as the gold standard. In that study, 200 patients with biochemically confirmed PA were either randomized to further care based on CT scans, that is, unilateral adrenalectomy in the case of a unilateral adrenal mass of at least 7 mm or otherwise MRA therapy, or on AVS, that is, unilateral adrenalectomy in the case of lateralization on the AVS or otherwise MRA therapy.[65] There was no difference between the groups with respect to the main clinical outcomes of this trial,

but its publication was followed by an intense discussion, with criticism regarding, for instance, its generalizability, validity, or statistical power.[66] Therefore, and due to multiple observational data suggesting the superiority of AVS-based vs CT--based treatment of PA, many experts continue to recommend AVS over CT scans to guide further treatment of the disease.[5,66] As in evidence-based medicine randomized controlled trials (RCTs) should have a higher impact on patient care than observational studies, we are of the opinion that the CT-based management of PA patients as performed in the SPARTACUS trial can be considered in routine clinical care, particularly in severe PA cases with a desire for surgery and no availability of AVS or other functional imaging methods. The main question in this setting is not whether AVS-based management is superior to CT-based management, but whether precluding surgery in potential candidates is justified in high-risk patients (in particular those with suppressed renin levels despite MRA treatment) if AVS is not available or not reliably performed in a local hospital. It is worth mentioning that prediction of the PA subtype is still possible when AVS is only unilaterally successful if contralateral suppression of aldosterone secretion is present.[67]

Several nuclear molecular imaging methods have been described that may aid in the subtype classification of PA, as they provide functional information on adrenal lesions.[68] Of note, a recent prospective study in 143 patients with PA documented that ^{11}C-metomidate positron emission tomography (PET) / CT (MTO) scanning following pretreatment with dexamethasone enables noninvasive detection of unilateral APAs, and is at least as accurate as AVS.[69] MTO can therefore be considered instead of AVS, but the main limitation of ^{11}C-MTO is its 20-minute half-life, which requires synthesis in an on-site cyclotron.[69] Therefore, ^{18}F ligands, with a 2-hour half-life, are currently under investigation for this PA imaging method, and could thus serve as a more widely available and better transportable ligand for most hospitals with PET imaging facilities in the near future.[69,70]

Clinical decisions on whether to proceed with aggressive and resource-demanding subtype classifications of PA or to bypass them by proceeding with CT-based management may be guided by clinical prediction scores that aim to aid in the differentiation between unilateral and bilateral forms of PA.[71-74] Their diagnostic accuracy in validation studies is limited, but a rough guidance for clinicians could be that serum potassium within the normal range, only slightly elevated ARR, and / or slightly elevated PAC after confirmatory tests, and a lack of unilateral tumor on CT make the diagnosis of a surgically curable PA rather unlikely, and vice versa.[73]

Medical therapy of primary aldosteronism Regardless of the diagnosis of PA, MRAs are the recommended fourth-line treatment in patients with resistant hypertension (ie, those on 3 different antihypertensive drugs not achieving the target BP levels), according to the current guidelines.[2] In this context, the randomized controlled PATHWAY-2 trial[75] documented that in resistant hypertensive patients without apparent PA, spironolactone was superior to bisoprolol or doxazosin as an add-on drug to lower BP in this setting. In mechanistic substudies of this RCT, it was shown that the higher the ARR, the higher the BP-lowering effect of spironolactone in these patients.[76]

In general, medical therapy of PA should be accompanied by dietary sodium restriction, which, if effective, can result in volume contraction and a rise in renin concentration, with normalization of ARR and BP in milder phenotypes.[77] On the other hand, salt potentiates the detrimental cardiovascular effects of aldosterone excess.[62]

The classic medical treatment of PA is spironolactone. It is a steroidal derivative of progesterone that competitively antagonizes the MR.[62] Of note, food increases the bioavailability of spironolactone and the BP-lowering effects manifest slowly, reaching their maximum after about 3 to 4 weeks of treatment.[62] The usual starting dose of spironolactone is 25 mg daily (occassionally, 12.5 mg daily).[78] Some experts argue that a spironolactone dose of 50 mg (or just slightly higher but not exceeding 75 mg) per day may be sufficient for most PA patients.[62,78] Higher doses may be required for some PA patients but also increase the risk of adverse effects, in particular due to sex-hormone receptor interactions, with gynecomastia, breast tenderness, low libido, or menstrual cycle irregularities. Therefore, it is not recommended to exceed a daily dose of 100 mg.[78] Eplerenone is a selective MRA with an efficacy roughly half of that reported for spironolactone (eg, 50 mg spironolactone equals about 100 mg eplerenone daily). Eplerenone can be used in the case of antiandrogenic side effects, but it requires at least a twice daily intake due to a shorter half-life.[62] The ENaC inhibitors, amiloride and triamterene, can also be considered as alternative or adjunct treatment for PA, but they are not capable of blocking several of the BP-independent adverse MR-mediated effects. Among nonsteroidal MRAs, esaxerenone has recently shown favorable effects and safety profile without adverse effects in patients with PA in a multicenter, open-label study; however, it is currently available only in Japan.[62,79] Aldosterone synthase inhibitors are promising candidates for future treatment approaches, and baxdrostat showed excellent antihypertensive effects in an RCT in treatment-resistant hypertension.[62,80]

There is no clear recommendation for clinicians on how to dose-titrate medical therapy for PA and how to reduce other antihypertensive drugs in this setting, but measurements of potassium and creatinine 7 to 10 days after starting spironolactone and potential dose titration in steps of 25 mg in 4-week intervals, along with simultaneous measurements of potassium and

TABLE 4 Consensus regarding outcome measures after unilateral adrenalectomy for primary aldosteronism

Initial evaluation should be done after 3 months but final evaluation should take place 6–12 months after the surgery, and then annually.
Complete clinical success: normal BP without antihypertensive medications
Partial clinical success: the same BP as before the surgery with either fewer antihypertensive medications or a reduction in BP with either the same number or fewer antihypertensive medications
Absent clinical success: unchanged or increased BP with either the same number or more antihypertensive medications
Complete biochemical success: correction of hypokalemia (if present presurgery) and normalization of the ARR
Partial biochemical success: correction of hypokalemia (if present presurgery) and a raised ARR with 1 or both of the following (as compared with presurgery): at least 50% decrease in baseline aldosterone concentration or abnormal but improved postsurgery confirmatory test result
Absent biochemical success: persistent hypokalemia (if present presurgery) or persistent raised ARR, or both, with failure to suppress aldosterone secretion with a postsurgery confirmatory test

Abbreviations: BP, blood pressure; others, see **TABLE 1**

creatinine, have been proposed.[78] As a rough guidance, the general treatment goals are to decrease (normalize) BP, increase (normalize) serum potassium (or, eg, aim for a level of 4–5 mmol/l), and achieve a rise in renin level along with a decline in the ARR.[45,62] It must be stressed that in observational studies, achieving an unsuppressed renin level with MRA treatment in PA patients reduced the increased cardiovascular risk (eg, for cardiovascular events or mortality) in PA patients to the level of controls with essential hypertension, but this effect was not observed in the PA patients with remaining renin suppression under ongoing MRA therapy.[37,38,62] Based on the current evidence, Vaidya et al[51] proposed that an increase in plasma renin activity greater than 1 ng/ml/h (which approximates direct renin concentrations >10 mU/l) is an ideal target for MRA treatment of PA patients with an unclear upper limit for renin (levels above the reference range may probably indicate overtreatment); however, it is likely that any increase in renin levels from the baseline status is indicative of a beneficial MR blockade.[51,62] Of note, clinicians must be aware of the risk of hyperkalemia with MRA treatment, particularly in patients with chronic kidney disease, and must therefore regularly monitor serum potassium levels.

There is still an ongoing debate on whether surgical treatment of PA is superior to MRA treatment. Some observational studies showed comparable outcomes of these 2 treatment modalities, whereas others documented improved outcomes with adrenalectomy evidenced by, for example, reduced cardiovascular events, reduced mortality, or improved quality of life.[36,39,40,81-86] There are no RCTs addressing this research question but it is tempting to speculate that when renin concentration increases to the levels suggested above, there may be no significant additional benefit of surgery in terms of hard clinical outcomes. Thus, subtyping is not sensible in a PA patient with unsuppressed renin on MRA treatment who has no imperative wish for surgery, as the medical treatment can be considered sufficient, with no need for further diagnostics. Nevertheless, successful surgical treatment of PA may obviate the need for lifelong MRA treatment and may definitely cure the disease.

Surgical therapy and radiofrequency ablation Surgical treatment is recommended for patients with unilateral PA who are healthy enough and willing to undergo surgery.[51] Presurgical treatment with MRAs is useful to optimize perioperative BP, normalize serum potassium, and lower the incidence of postoperative hyperkalemia (potentially mediated by increasing renin concentration and restoring the function of the contralateral adrenal gland).[87] Complete adrenalectomy via laparoscopic or retroperitoneoscopic approach is preferred over partial adrenalectomy whenever segmental sampling during AVS is not available, because the source of aldosterone secretion from a single adrenal gland may not be due to a visible adrenal adenoma but possibly also due to, for example, aldosterone-producing micronodules. Postoperatively, potassium supplements and potassium-sparing medications (ie, ACEIs, ARBs, or MRAs, ENaC inhibitors) should be immediately stopped and regular measurements of serum potassium (eg, weekly for 4 weeks) should be performed.[22] BP improves gradually over 1 to 3 months after surgery, and requires close monitoring with adjustment of antihypertensives. Standardized criteria according to the PASO (Primary Aldosteronism Surgical Outcome) study[30] have been published on the outcome after adrenalectomy for unilateral PA (**TABLE 4**). In that study, complete and partial clinical success, and complete biochemical success after unilateral adrenalectomy was achieved in 37%, 47%, and 95% of the PA patients, respectively.[30] Determinants of clinical benefit were younger age, female sex, lower body mass index, higher systolic BP, and more antihypertensive medications at baseline.[30] Interestingly, an international retrospective cohort study documented that unilateral adrenalectomy had a clinical benefit (ie, complete or partial clinical success) in 81% of AVS-proven bilateral PA patients.[88] This finding challenges the current dogma of routine MRA treatment in bilateral disease and speaks in favor of unilateral adrenalectomy to attenuate the severity of PA in patients with grossly asymmetric disease, known cardiovascular or chronic kidney disease, young age, suboptimal MRA therapy, or burdensome polypharmacy.[89]

Clinicians should be aware that the PA-associated glomerular hyperfiltration normalizes after successful treatment and may therefore unmask renal damage (and thus should not be considered a treatment complication). A systematic review showed that after a median follow-up of 12 months, a reduction in estimated glomerular filtration rate by 10.69 ml/min/1.73 m^2

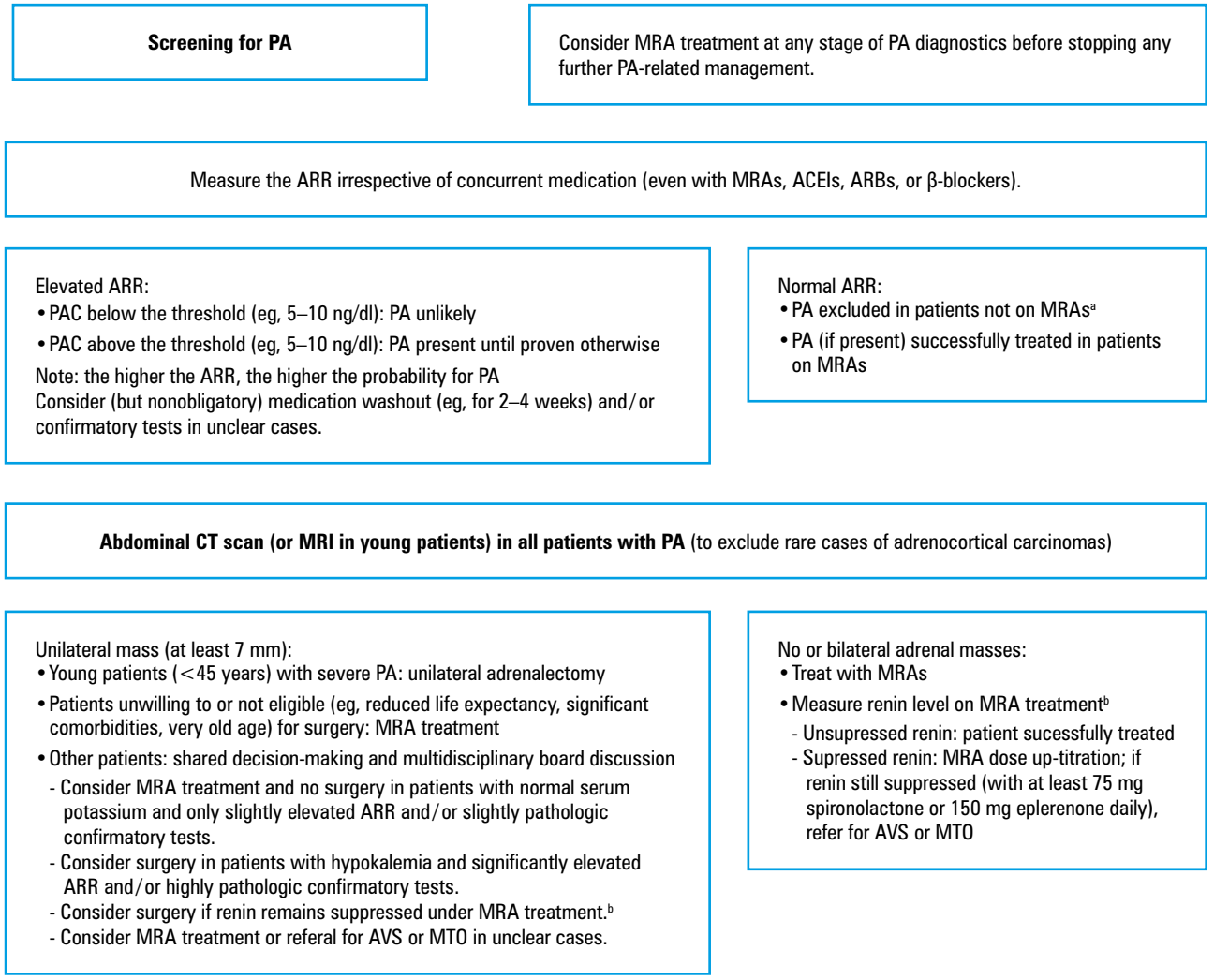

FIGURE 1 Proposed management of primary aldosteronism diagnostics and treatment for nonexpert centers and/or in the case of limited resources

a Mild PA still possible: in the case of a strong clinical suspicion and expected treatment benefit for the patient, stop and eventually replace interfering medications, then retest.

b Increase in plasma renin activity >1 ng/ml/h (which approximates direct renin concentrations >10 mU/l) is an ideal target for MRA treatment.

Abbreviations: AVS, adrenal venous sampling; CT computed tomography; MRAs mineralocorticoid receptor antagonists; MRI magnetic resonance imaging; MTO, ^{11}C-metomidate positron emission tomography/computed tomography; PA, primary aldosteronism; others, see TABLES 1 and 3

(95% CI, –13.23 to –8.16) was observed in both medically and surgically treated PA patients.[35] In APA patients, cosecretion of cortisol evidenced by the 1-mg dexamethasone suppression test is common (eg, one-third of patients in a study from Spain), but the implications of this for surgical patient outcomes are unclear at the moment, except for postoperative adrenal insufficiencies (AIs).[90] On the other hand, patients with PA seem not to require routine evaluation for AI if concurrent hypercortisolism has been excluded preoperatively.[91]

Several case reports and small cohort studies reported on the successful use of radiofrequency ablation (RFA) for the treatment of unilateral PA.[92] Current evidence comparing RFA with unilateral adrenalectomy for the treatment of PA is limited and variable.[92] Given that RFA is less invasive than laparoscopic surgery and thus associated with lower postoperative analgesia, reduced length of hospital stay, and earlier return to work, it can be considered a promising new treatment approach, at least for selected patients.[92]

Public health perspective of primary aldosteronism

The high prevalence and disease burden of PA, which is largely not recognized and often not sufficiently treated in affected patients, is of great public health concern.[3,93] It has been estimated that less than 1% of all PA cases are detected, and this is in line with surveys showing extremely low PA screening rates in primary care.[3,87,94-96] Limited awareness of PA among general practitioners (GPs) may not be the main reason for this underdiagnosis of PA, as screening rates were still low among GPs informed about PA.[97] Switching antihypertensive medications for the purpose of ARR testing was identified as a significant barrier to PA screening, and GPs, although well aware of PA, see less value in screening patients with mild hypertension.[97,98] Educating GPs that PA screening can also be done without altering RAAS-interfering drugs and that PA treatment is particularly effective in early stages of the disease (ie, in young patients), before end-organ damage ensues, may lead to reducing this screening gap,

and reimbursement of the ARR tests may also be important.[30] Future guidelines for diagnosis and treatment of PA should seriously aim to improve the practical implementation of their recommendations into daily clinical routine, as this is an important quality criterion of any clinical guideline.[7] This challenging task must take into account that tools with less diagnostic accuracy but higher potential for broader implementation in everyday practice may be superior for the improvement of public health over high-end but complex and resource-demanding approaches. Harmonization of diagnostic approaches for PA is also crucial, as high diversity in the screening and confirmatory testing for PA prevails even among expert centers.[99]

Conclusions We summarized the current state of the art regarding the diagnosis and treatment of PA and outlined pragmatic approaches for clinicians on how to take care of patients when facing insufficient resources and expertise for performing time-consuming and costly diagnostic tests for PA, including AVS. Our considerations and suggestions for the management of PA diagnostics and treatment for nonexpert centers or if resources are limited are outlined in **FIGURE 1**. Finally, we wish to re-emphasize the importance of screening and treating PA to reduce the enormous public health burden of this disease. We hope that in concert with nonprofit organizations, such as the Primary Aldosteronism Foundation (https://www.primaryaldosteronism.org), this article will help achieve this goal.[100]

ARTICLE INFORMATION

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