Primary Aldosteronism: State-of-the-Art Review

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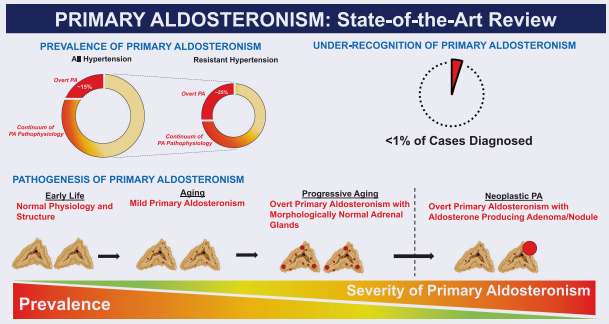
We are witnessing a revolution in our understanding of primary aldosteronism (PA). In the past 2 decades, we have learned that PA is a highly prevalent syndrome that is largely attributable to pathogenic somatic mutations, that contributes to cardiovascular, metabolic, and kidney disease, and that when recognized, can be adequately treated with widely available mineralocorticoid receptor antagonists and/or surgical adrenalectomy. Unfortunately, PA is rarely diagnosed, or adequately treated, mainly because of a lack of awareness and education. Most clinicians still possess an outdated understanding of PA; from primary care physicians to hypertension specialists, there is an urgent need to redefine and reintroduce PA to clinicians with a modern and practical approach. In this state-of-the-art review, we provide readers with the most updated knowledge on the pathogenesis, prevalence, diagnosis, and treatment of PA. In particular, we underscore the public health importance of promptly recognizing and treating PA and provide pragmatic solutions to modify clinical practices to achieve this.

GRAPHICAL ABSTRACT



Keywords: adrenal; aldosterone; blood pressure; hypertension; primary aldosteronism; renin.

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INTRODUCTION AND CLINICAL PATHOPHYSIOLOGY

The past 20 years have witnessed a revolution in our understanding of primary aldosteronism (PA). PA is a pathologic form of aldosteronism, characterized by renin- and angiotensin II-independent aldosterone production that is relatively nonsuppressible. This PA pathophysiology can manifest across a broad continuum; thus, PA is best considered a *syndrome* rather than a binary disease. Once considered to be a rare hormonal cause of hypertension, we now recognize that the PA syndrome is common, and contributes to cardiovascular and kidney disease. Insights into the pathogenesis of PA have shown that it is largely driven by pathogenic somatic mutations that may progressively accrue across the lifespan, and occasionally merge with neoplasia to create the most severe forms of neoplastic PA. In parallel, prevalence studies have consistently shown that the prevalence of overt and categorically classified PA ranges from 10% to 25% in the hypertensive population. However, beyond this categorical definition of PA, we now understand that there is an expansive continuum of PA pathophysiology (relatively nonsuppressible and renin-independent aldosterone production) that exists beyond this categorical construct. Unfortunately, the reality is that fewer than 1% of patients with overt PA are ever diagnosed, largely due to a lack of awareness and testing, and virtually none of the patients with milder forms of PA pathophysiology are ever identified or treated. This constitutes an unrecognized public health crisis since PA pathophysiology can be treated

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with widely available targeted therapies that can mitigate the adverse health effects of PA.

In this state-of-the-art review, we aim to provide readers with a contemporary view of PA pathogenesis and epidemiology, while simultaneously sharing pragmatic approaches to diagnosis and treatment. It is our hope that after reading this review, readers will be informed and invigorated to improve clinical care for their patients by adapting to the new landscape of PA described herein.

THE PATHOGENESIS OF PA

Updates in the genetics and histopathology of PA

Significant progress has been made in determining the histopathologic and genetic characteristics of PA.[1,2] The development of specific antibodies against human CYP11B2 (aldosterone synthase) and its application to immunohistochemistry have facilitated the identification of sources of aldosterone production in surgically resected adrenal tissue,[3,4] revealing diverse histopathologic characteristics of adrenal glands from PA patients.[5,6] Recently, an international consensus for the nomenclature and definition of adrenocortical lesions from patients with unilateral PA was developed and endorsed by the World Health Organization.[7,8] Based on hematoxylin and eosin staining (for morphologic examination) and CYP11B2 immunohistochemistry (for functional characterization), the proposed classifications include: aldosterone-producing adenoma (APA), aldosterone-producing nodule (APN), aldosterone-producing micronodule (APM) (formerly known as "aldosterone-producing cell cluster"), aldosterone-producing diffuse hyperplasia, and rarely, aldosterone-producing adrenocortical carcinoma.[7] It is important to note that *multiple aldosterone-producing lesions can occur within a single adrenal gland*, and that adrenal lesions identified by imaging studies are not necessarily the source of aldosterone excess[9,10] (Figure 1). Incidental nonfunctioning adenomas can also commonly occur in patients with PA; in these cases, satellite APA or APN/APM in the adjacent or contralateral adrenal tissue may be the source of excess aldosterone production. The histopathology of PA when there is concomitant hypercortisolism can also be variable. The conceivable histologic subtypes include: an aldosterone and cortisol coproducing adenoma,[11,12] a dominant cortisol-producing adenoma with multiple APMs in the adjacent adrenal tissue,[13,14] and coexistence of separate APA and cortisol-producing adenoma.[15–19] Multiple APMs appear to be a common histologic feature of idiopathic hyperaldosteronism (or bilateral PA).[20]

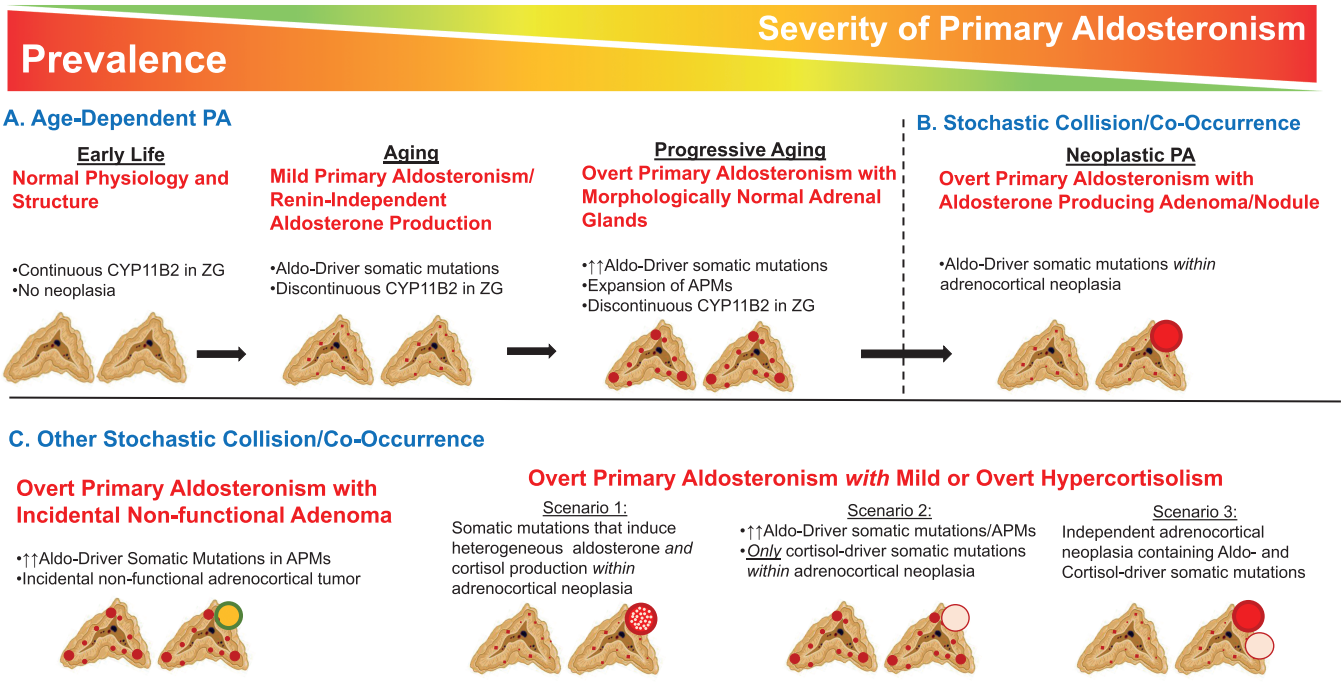

Figure 1. Models for the pathogenesis of primary aldosteronism. (**a**) Young human adrenals display a continuous pattern of CYP11B2 expression in the *zona glomerulosa*. With aging, CYP11B2 expression becomes discontinuous, and there are greater numbers of aldosterone-producing micronodules (APMs), often harboring pathogenic aldosterone-driver somatic mutations; in parallel, there is greater renin-independent aldosterone production indicative of mild PA. With progressive aging, a proportion of individuals will have expansion of APMs, despite morphologically normal-appearing adrenal glands, contributing to overt PA. (**b**) Although the vast majority of PA is likely attributable to progressive acquisition of APMs and pathogenic somatic mutations, less commonly, these entities may co-occur or collide with adrenocortical neoplasia to form an APA. Although APAs manifest with the most severe PA clinical phenotype, they likely represent the minority of PA cases. (**c**) Other stochastic co-occurrences include the combination of APMs with incidental and nonfunctional adrenocortical neoplasia, and the combination of aldosterone production with cortisol production. Models of aldosterone and cortisol coproduction include (i) an aldosterone and cortisol coproducing adenoma; (ii) a cortisol-producing adenoma with a background of APMs; and (iii) separate cortisol- and aldosterone-producing adenomas. Abbreviations: Aldo, aldosterone; APA, aldosterone-producing adenoma; PA, primary aldosteronism; ZG, *zona glomerulosa*. (Figures created in BioRender.com.).

The application of next-generation sequencing has resulted in the detection of disease-causing somatic and germline mutations in APA and familial hyperaldosteronism (FH), respectively. The affected genes encode ion channels: *Potassium Inwardly Rectifying Channel Subfamily J Member 5* (*KCNJ5*),[21] *Calcium Voltage-Gated Channel Subunit Alpha1 D* (*CACNA1D*),[22] *Calcium Voltage-Gated Channel Subunit Alpha1 H* (*CACNA1H*),[23,24] and *Chloride Voltage-Gated Channel 2* (*CLCN2*)[25,26] and ATPases: *ATPase* Na^+/K^+ *Transporting Subunit Alpha 1* (*ATP1A1*) and *ATPase Plasma Membrane* Ca^{2+} *Transporting 3* (*ATP2B3*).[27] Aldosterone-driver mutations in these genes either directly or indirectly (via cell membrane depolarization) increase intracellular calcium levels that stimulate aldosterone synthase (*CYP11B2*) expression and aldosterone production. Activating somatic mutations in exon 3 of the *CTNNB1* gene that encodes β-catenin have also been identified in a small subset of APA.[28,29] *CTNNB1*-mutated tumor cells may require a second somatic mutation to obtain the capacity to produce aldosterone. For example, concomitant mutations in *GNAQ/11*[30] or *CACNA1D* genes[31] have been reported in *CTNNB1*-mutated APAs. Inheritable causes of PA are rare. FH-I is caused by the presence of a chimeric gene resulting from an unequal crossing over between *CYP11B1* (11β-hydroxylase, the cortisol biosynthetic enzyme) and *CYP11B2* genes, leading to abnormal aldosterone production that is regulated by adrenocorticotropic hormone (ACTH).[32] Germline pathogenic variants in *CLCN2*,[25,26] *KCNJ5*,[21] and *CACNA1H*[24] have been identified as responsible for FH-II, FH-III, and FH-IV, respectively. *De novo* germline variants in the *CACNA1D* gene have also been identified as the cause of the rare PASNA syndrome (PA, seizures, and neurologic abnormalities).[22]

Although genetic causes of PA with hypercortisolism are not fully understood, some studies have shown somatic *KCNJ5* mutations in adrenal tumors from such patients (presumably aldosterone and cortisol coproducing adenoma).[12,33,34] The capacity to produce both aldosterone and cortisol may partly be explained by coexpression of steroidogenic enzymes CYP11B2 and CYP11B1 (11β-hydroxylase) in *KCNJ5*-mutated APA.[35–39] Somatic mutations in *PRKACA* and *GNAS*, both known as genetic causes of cortisol-producing adenoma, have also been reported in adrenal tumors from patients with PA and autonomous cortisol secretion[40,41]; however, the pathologic role of these mutations needs further investigation.[15,18,31]

While heritable forms of PA are rare, somatic mutations causing PA are common. Using the combination of CYP11B2 immunohistochemistry (to identify lesions for DNA capture) and next-generation sequencing, pathogenic somatic mutations have been identified in approximately 90% of APAs.[31,37,42] There appear to be sex and racial differences in the prevalence of somatic mutations in APA; for example, *KCNJ5* is more common in East Asians and women regardless of race.[43] Among these aldosterone-driver somatic mutations, *CACNA1D* mutations have frequently been documented in APMs in adrenals with bilateral or idiopathic aldosteronism[20] as well as in normal adrenals.[44,45] One important caveat on interpreting prevalence and demographic characteristics of somatic mutations is the multiple biases resulting in case detection and surgical adrenalectomy, which may skew the findings from available tissues in unpredictable ways.

Aging and adrenal histopathology

In 2010, Nishimoto *et al.*[3] developed polyclonal antibodies that could independently detect human CYP11B1 and CYP11B2. Using these antibodies, the authors defined 2 distinct patterns of functional adrenocortical zonation, (i) conventional zonation with sporadic CYP11B2-positive cells in the *zona glomerulosa* (ZG) and (ii) variegated zonation with subcapsular CYP11B2-expressing cell clusters, termed aldosterone-producing cell clusters (recently redefined as APMs). Four years later, Gomez-Sanchez *et al.*[4] successfully generated and characterized highly specific monoclonal CYP11B1 and CYP11B2 antibodies (RRID: AB_2650563 and AB_2650562, respectively). Since then, these monoclonal antibodies have been widely used for research and are currently commercially available.

To study CYP11B2 expression patterns in normal physiology, adrenal glands from deceased kidney donors and autopsy cases have been used. Using these specimens, 3 independent studies have demonstrated age-dependent accumulation of APMs,[45–47] thereby implicating an age-dependent PA pathophysiology. In contrast, continuous zonal CYP11B2 expression in the ZG appears to be a feature of young adrenals that progressively dissipates with age.[46,47] Aldosterone-driver somatic mutations, especially in the *CACNA1D* gene, are frequently found in APMs in normal adrenals, suggesting that an acquisition of pathogenic somatic mutations and APMs induces an age-dependent renin-independent aldosterone production.[44,45,47,48] Dysregulated aldosterone production by APM has been further supported by mass spectrometry-based imaging analysis.[49,50]

Origins of PA

Considerable effort has been made to determine the cellular origins of PA. The number of APM per adrenal is significantly higher in patients with idiopathic aldosteronism or cross-sectional image-negative unilateral PA compared with normal adrenals.[20,45] These histopathologic findings may explain the continuum of renin-independent aldosterone production that parallels the severity of clinical phenotypes.[51]

It is of great interest whether APM is a precursor of APA, as APM frequently harbor aldosterone-driver mutations. Some researchers have proposed an APM to APA progression model based on the observation of adrenocortical lesions termed, "possible APM-to-APA translational lesions," that contains histologic features of both APM and APA.[52,53] One *in situ* mass spectrometry imaging study revealed 2 distinct metabolic phenotypes of APM wherein 1 had a similar metabolic phenotype to APA, suggesting that a subset of APM may have the capacity to transition to APA.[54] A possible 2-hit model of pathophysiologic convergence has also been proposed as an alternative hypothesis of APA development. In this model, abnormal cell proliferation due to genetic or environmental factors (neoplasia) occurs

with somatic mutations in aldosterone-driver genes (aldosterone production).[2,55,56] This latter model suggests that the high prevalence of PA is largely driven by a diffuse, bilateral, and nonneoplastic process of acquired pathogenic somatic mutations that likely result in mild-to-moderate PA pathophysiology. In a minority of cases, this process (and a parallel process inducing cortisol production) can collide with adrenocortical neoplasia to permit the emergence of more severe and overt cases of PA (Figure 1). Finally, it is important to note that beyond these pathogenic mutations and histopathologic morphologies, other circulating and paracrine factors, including ACTH, angiotensin II, LH/GnRH, GIP, vasopressin, leptin, serotonin, and mast cell activity, also play an important and variable role in determining the dysregulated production of aldosterone by activating their overexpressed, or ectopically expressed, receptors in PA tissues.[57–70]

EPIDEMIOLOGY AND PREVALENCE

The prevalence of PA is considerably higher than previously realized (Figure 2).[71] Several considerations that influence diagnostic interpretations account for the wide range of reported prevalence estimates. Although the diagnosis of PA has typically been made using relatively arbitrary categorical thresholds, growing evidence suggests that PA exists across a broad continuum.[51,72–77] Thus, the reliance on specific categorical thresholds can yield dramatically different estimates of prevalence. For example, requiring an aldosterone-to-renin ratio (ARR) of >30 ng/dl per ng/ml/h as well as an aldosterone level >10 ng/dl to be considered a "positive" screen identifies 13.8% of hypertensive patients as potentially having PA; however, liberalizing these thresholds to an ARR >20 and omitting any requirement for a minimum aldosterone concentration can increase this yield to 33%.[78,79] Similarly, using an aldosterone excretion rate of >10 μg/24 hours following an oral sodium loading test classifies up to 34% of patients with stage 2 hypertension as having PA, whereas using a threshold of >12 μg/24 hours only identifies 21.6%.[51] These 2 examples highlight how the arbitrary reliance on categorical thresholds can distract clinicians from realizing the full spectrum of PA and its high prevalence.[80] Herein, we will consider "overt" PA to describe PA defined by traditional categorical thresholds and to facilitate reporting of prevalence estimates; however, we also discuss in this review that overt PA represents the most severe extreme of the broad spectrum of PA that contributes to adverse health outcomes.

In individuals *without* hypertension, the prevalence of overt PA is estimated to be 11%–14%.[51,74,76] The clinical significance of this unrecognized burden of overt PA among normotensive individuals is that it identifies those at increased risk for developing hypertension in the future.[72–75] Among patients with hypertension evaluated in the primary care or community setting, prevalence estimates for overt PA range from 0.7% to 14%,[78,81–85] with higher prevalence paralleling greater hypertensive severity (3.9% in stage 1, 9.7% in stage 2, and 11.8% in stage 3).[78] Notably, in a prospective study of untreated Australian patients with newly diagnosed hypertension, 25% had an elevated ARR and at least 14% (and up to 21%) were diagnosed with overt PA.[82] These results are akin to the 15.7% prevalence reported in an untreated American cohort with stage I hypertension,[51] thereby providing reproducible and consistent prevalence estimates.

In patients with hypertension and hypokalemia referred to specialty hypertension care, 28.1% had overt PA, though this increased to as much as 88.5% in the subgroup with severe hypokalemia.[86] In referral centers for hypertension and among patients with resistant hypertension, estimates of prevalence range from 4.0% to 30%,[51,87–94] and when patients with both resistant hypertension and renin suppression are considered, up to 50% may have overt PA.[51]

CLINICAL OUTCOMES AND PUBLIC HEALTH RELEVANCE

Without targeted treatment, PA results in disproportionately high rates of cardiovascular, kidney, and metabolic disease compared with essential hypertension (Table 1).

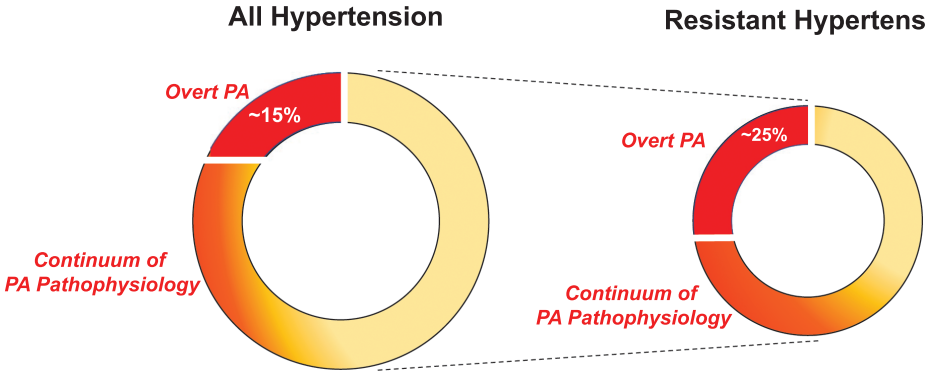

Figure 2. The prevalence of primary aldosteronism. The prevalence of "overt PA" among untreated and/or new patients with hypertension has been reported to be as high as 14%–15% when using liberalized diagnostic interpretations; however, the prevalence of milder forms of PA pathophysiology is much higher. Among the subset of hypertensive individuals with resistant hypertension, the prevalence of "overt PA" is at least 25%, although when employing more liberalized criteria to define overt PA, it could be as high as 50%. Beyond this categorical definition of PA, there exists a broad continuum of "PA pathophysiology" in resistant hypertension, providing 1 reason why MR antagonists are especially effective in this situation. Abbreviations: MR, mineralocorticoid receptor; PA, primary aldosteronism.

Table 1. Long-term health impact of primary aldosteronism prior to targeted treatment

Long-term health impact of primary aldosteronism
Cardiovascular disease risk
Coronary artery disease
Congestive heart failure
Left ventricular hypertrophy
Atrial fibrillation
Stroke
Cardiovascular mortality
Kidney disease risk
Glomerular hyperfiltration
Accelerated decline in glomerular filtration rate
End-stage kidney disease
Proteinuria
Metabolic disease risk
Type 2 diabetes mellitus
Metabolic syndrome/obesity
Obstructive sleep apnea
Osteoporosis/fractures

While greater blood pressure elevation in PA may partially explain some of this excess risk, the increased rates of adverse outcomes are also independent of blood pressure. These blood pressure-independent effects are attributed to deleterious mineralocorticoid receptor (MR) activation in extrarenal tissues such as the myocardium and vascular endothelial and smooth muscle cells, resulting in fibrosis, necrosis, and endothelial dysfunction.[95–112] Animal and human studies have shown that the combination of sodium/volume loading with excess aldosterone–MR interactions causes cardiovascular and kidney disease that can be mitigated by either restricting dietary sodium or by treatment with MR antagonists.[113–116]

Numerous observational studies have demonstrated higher rates of adverse cardiovascular outcomes in patients with overt PA.[78,117–131] A meta-analysis synthesizing the results from many of these observational studies reported that overt PA was associated with a higher risk of coronary artery disease (odds ratio [OR] 1.77 [95% confidence interval, CI 1.10–2.83]), heart failure (OR 2.05 [95% CI 1.11–3.78]), left ventricular hypertrophy (OR 2.29 [95% CI 1.65–3.17]), atrial fibrillation (OR 3.52 [95% CI 2.06–5.99]), and stroke (OR 2.58 [95% CI 1.93–3.45]).[132] In addition, several observational studies have also reported a heightened cardiovascular mortality risk associated with overt PA compared with essential hypertension.[123,125]

Despite the historical focus on its cardiovascular impact, PA also contributes to a number of noncardiovascular adverse outcomes. PA causes glomerular hyperfiltration leading to increased glomerular filtration rate.[133] As with other disease processes that result in glomerular hyperfiltration (e.g., diabetic nephropathy, obesity), this ultimately leads to a steeper longitudinal decline in glomerular filtration rate along with higher rates of incident chronic kidney disease and albuminuria.[134–141] Moreover, PA is associated with an increased risk of type 2 diabetes mellitus and metabolic syndrome.[125,142–145] This may be attributable to both decreased insulin secretion and increased insulin clearance in PA,[146] as well as to concurrent cortisol cosecretion.[142] Not surprisingly given its association with obesity and the pathophysiology of chronic volume retention, PA frequently co-occurs with obstructive sleep apnea.[147–149] Prevalence estimates of obstructive sleep apnea in patients with PA range from 21% to 34%.[150–152] Finally, PA increases the risk for both osteoporosis and fractures, possibly mediated by hypercalciuria-induced secondary hyperparathyroidism.[153–156]

Numerous population- and community-based cohort studies have also highlighted that even milder phenotypes of PA pathophysiology (that is renin-independent aldosterone production that lies below the categorical thresholds for overt PA), are independently associated with the development or progression of cardiovascular and kidney disease. Once hypertension has developed, the magnitude of PA pathophysiology is associated with risk for worsening hypertension, incident structural heart disease, adverse cardiovascular events, and death.[77,157–159] PA pathophysiology is associated with lower renal plasma flow,[134,160] and among individuals with established chronic kidney disease, the magnitude of aldosterone production is associated with lower serum potassium, greater kaliuresis, and accelerated chronic kidney disease progression to end-stage kidney disease.[161]

Thus, while the categorical construct of "overt PA" may be convenient for estimating prevalence in research studies, and in developing clinical practice guidelines, this categorization fails to recognize the large and clinically relevant spectrum of milder PA. This lack of recognition is particularly alarming given that even overt PA is rarely diagnosed.

UNDER-RECOGNITION AND APPROACH TO DIAGNOSIS

Despite its substantial clinical and public health implications, PA remains highly underdiagnosed. Uptake of guideline screening recommendations is abysmally low and approaches zero. Most recommendations suggest screening several high-risk populations in which PA prevalence is known to be high (Table 2).[162–164] Yet numerous studies across the world consistently show that the overwhelming majority of patients meeting these criteria are never screened for PA (Figure 3).[165–171] For instance, a mere 1.6% of patients with resistant hypertension who are followed in the United States Veterans Affairs Health System received guideline-recommended PA screening.[169] Similarly, only 1.6% of patients in Ontario, Canada with hypertension and hypokalemia were screened for PA; even among those with hypertension and 5 or more episodes of hypokalemia, screening rates still remained below 5%.[170] These alarmingly low rates of testing speak to the general lack of awareness throughout the medical community about the prevalence and health impact of PA, and imply that the vast majority of overt PA remains undiagnosed and untreated.

Table 2. Populations considered to be "high-risk" for primary aldosteronism: high-risk populations are those in whom it has been demonstrated that the prevalence of primary aldosteronism is very high and mostly unrecognized

High-risk populations
Severe or resistant hypertension
Unexplained or diuretic-induced hypokalemia
Hypertension with adrenal mass
Hypertension with sleep apnea
Hypertension with atrial fibrillation
Strong personal or family history
Debated expansion of eligible populations
New-onset hypertension
Stage 2 hypertension
All hypertension

We suggest that all of these individuals be screened for primary aldosteronism. Beyond these high-risk individuals, there is growing consensus that screening for primary aldosteronism should be expanded to include more populations.

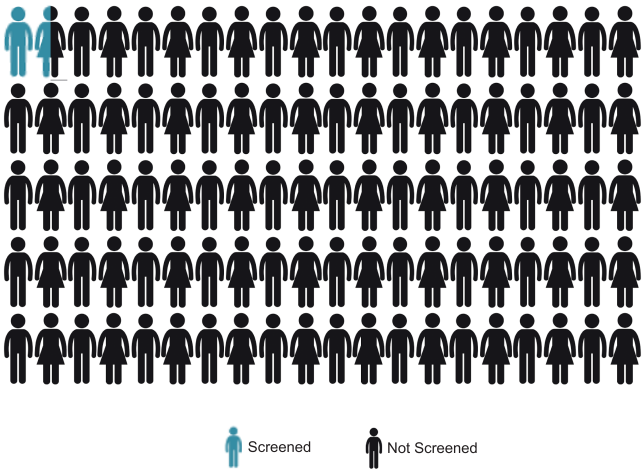

Figure 3. Abysmal screening rates for PA: numerous studies from across the world have consistently shown that at best, even among high-risk populations, screening rates for PA are below 2%. This implies that much fewer than 1% of high-risk patients are ever diagnosed with PA. Abbreviation: PA, primary aldosteronism.

Who and how to screen

"High-risk" or "high prevalence" patient populations with the greatest risk for having PA should be screened (Table 2); however, there is growing momentum to consider testing every patient with hypertension at least once as a part of standard care.[82,172]

To maximize case detection and thus public health impact, we advocate a pragmatic approach that addresses the high prevalence of overt PA, the higher prevalence and unrecognized nature of a milder spectrum of PA,[51,173] and the abysmally low detection rates.[165,170] In a "high-risk" patient with a suppressed renin, the diagnostic mindset should be that the patient has "*PA until proven otherwise*." This approach is distinct from the stepwise approach often prescribed by guidelines that places emphasis (or burden) on clinicians to "confirm" the diagnosis. By reforming the approach to assume PA until proven otherwise in high-risk phenotypes, we favor increasing the probability of making clinical diagnoses and/or initiating empiric treatment with MR antagonists for a wider array of PA phenotypes (Figure 4).

Screening should occur irrespective of concurrent medications—including MR antagonists—or time of day to simplify the approach and maximize opportunities to test. When interpreting testing results, we suggest evaluating aldosterone and renin values independently, rather than relying on the integrated ARR alone.[79,134,174] If renin is suppressed in a high-risk patient, irrespective of medications, the results can be interpreted.[175,176] Renin suppression, representing volume expansion and downstream suppression of angiotensin II, can be conservatively defined as a plasma renin activity <1.0 ng/ml/h or corresponding plasma renin concentration <10 mU/l. Renin suppression despite the use of renin-angiotensin-aldosterone system inhibitors and diuretics, which are known to increase renin,[177] should enhance clinician confidence in the presence of nonsuppressible aldosterone production.

If renin is not suppressed but clinical suspicion for PA is high, then repeat testing after withdrawal of MR antagonists and/or epithelial sodium channel inhibitors for up to 4 weeks is advisable. Many clinicians recommend withdrawal of other (or all) antihypertensive agents (such as converting enzyme inhibitors, angiotensin-receptor blockers, and diuretics); however, we find that this approach is impractical and infrequently necessary if clinicians adopt our proposed recalibrated diagnostic approach (Figure 4).[177]

Interpretations of screening

False-negative interpretations that erroneously exclude the diagnosis are far more common than false-positive interpretations,[177,178] and several factors should be considered when evaluating results. First, there are systematic differences in the calibration of aldosterone assays. Several recent studies have demonstrated that aldosterone measurements by liquid chromatography–tandem mass spectrometry (LC–MS/MS), which is becoming more widespread, are 27%–87% lower when compared with immunoassay-based techniques.[179–188] In 1 study of healthy volunteers who underwent simultaneous testing with both assay types under controlled physiologic conditions, a median aldosterone concentration of 19.6 ng/dl by immunoassay corresponded to only 10.5 ng/dl by LC–MS/MS (~50% lower); similarly, a median ARR of 23.3 ng/dl per ng/ml/h using immunoassay was only 6.2 ng/dl per ng/ml/h using LC–MS/MS (~75% lower).[188] In a cohort of patients with resistant hypertension and overt PA, 1 quarter had a circulating aldosterone concentration <10 ng/dl by LC–MS/MS, a threshold below which most clinicians would have excluded the possibility of PA.[51] Similarly, among overt PA patients undergoing adrenal venous sampling (AVS), 13%–26% are reported to have supine aldosterone concentration below 5 ng/dl by LC–MS/MS.[189] Distinct, LC–MS/MS assay-specific cutoff values for the ARR and for aldosterone values during confirmatory

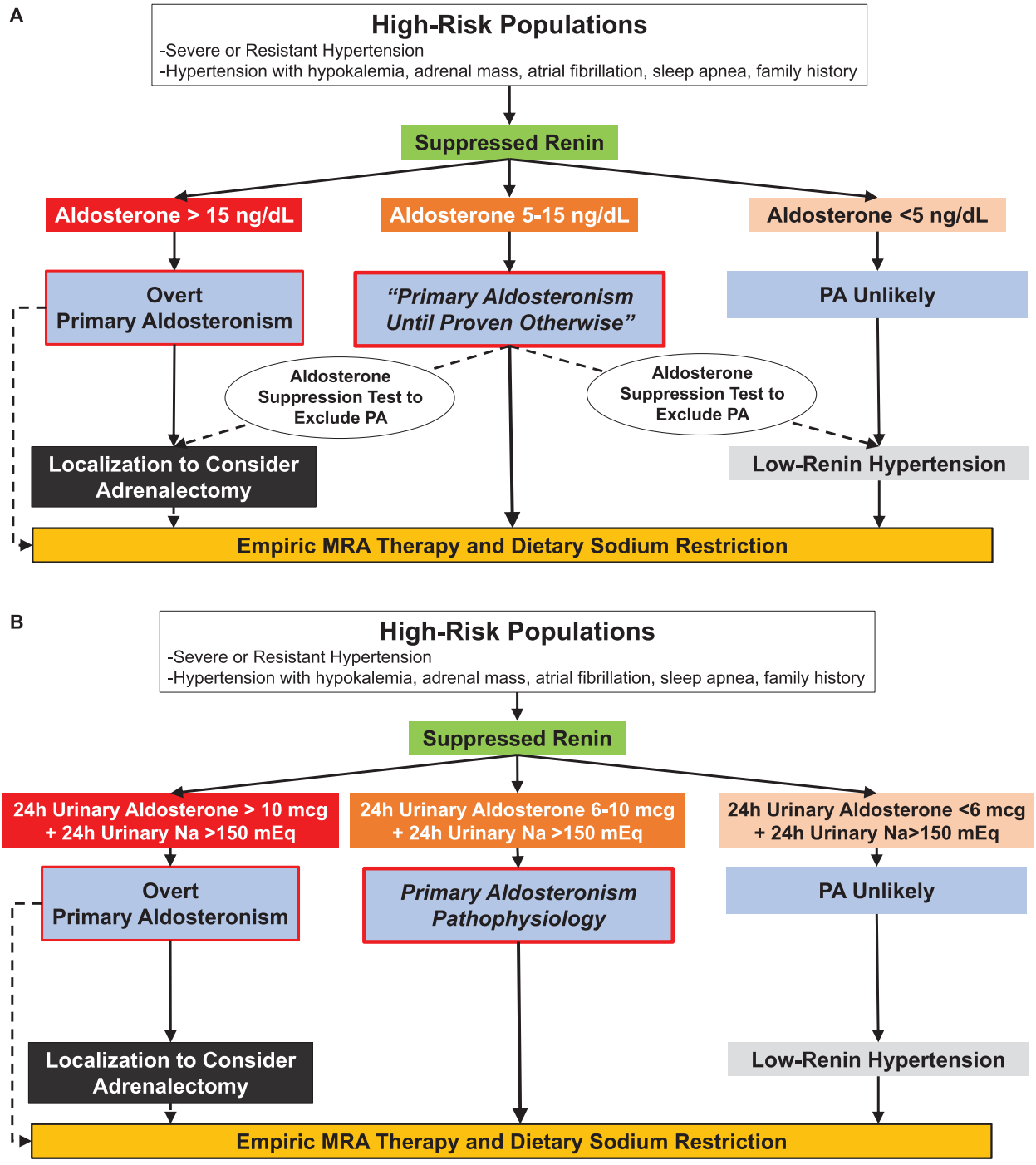

Figure 4. (**a**) Pragmatic diagnostic approach for all clinicians. High-risk populations are those with a high pretest probability for having PA. In the context of a suppressed renin, a plasma aldosterone >15 ng/dl essentially confirms the diagnosis of overt PA and clinicians can proceed to localization or empiric MR antagonist therapy. In a high-risk patient with a suppressed renin and a very low aldosterone concentration, <5 ng/dl, PA is unlikely; however, MR antagonist therapy should still be considered as an effective treatment for low-renin hypertension. For all other high-risk patients (suppressed renin and aldosterone 5–15 ng/dl), the diagnostic mindset should be that this is "*PA until proven otherwise*." Several options are available, including empiric initiation of MR antagonist therapy and dietary sodium restriction, or an aldosterone suppression test (including a 24-hour urine collection to measure aldosterone and sodium excretion) to exclude the possibility of PA or increase confidence in the diagnosis prior to pursuing localization and possible adrenalectomy. (**b**) Enhanced diagnostic approach for specialist clinicians. When available, specialists may opt to test high-risk populations with a suppressed renin with a 24-hour urine collection to gain a better integrated assessment of aldosterone production. This can be performed on an ad libitum diet since many patients may already be consuming sufficient dietary sodium, or after dietary sodium loading to ensure a high-sodium balance. Ideally, the desired 24-hour urinary sodium balance should be greater than 150 mEq/24 hours (reflective of a dietary intake of ~3.5 g of sodium per day). A 24-hour urinary aldosterone excretion rate of >10 mcg in this context likely confirms PA, whereas values between 6 and 10 mcg are suggestive of PA pathophysiology that is likely to still respond to targeted therapy. Twenty-four-hour urinary aldosterone excretion rates less than 6 mcg suggest PA is unlikely, but MR antagonist therapy may still be beneficial for low-renin hypertension. Abbreviations: MR, mineralocorticoid receptor; PA, primary aldosteronism.

Table 3. The advantages and disadvantages of PA testing using plasma and 24-hour urinary aldosterone measurements

	Plasma aldosterone	24-Hour urinary aldosterone
Variability	• Aldosterone production varies throughout the day; single spot plasma value may not reflect daily production • Risk for erroneous (false-negative) classification can be overcome by using liberalized thresholds for positive interpretation (see Figure 4a)	• Integrates aldosterone production throughout the day; less susceptible to daily variability • Only measures free and acid-labile aldosterone; does not adequately capture majority of aldosterone metabolites such as tetrahydroaldosterone that also reflect integrated production
Accessibility	• Venipuncture widely available • Assay for measurements generally widely available in locations where renin measurements also available	• 24-Hour urine collection capabilities less widely available when compared with venipuncture
Patient perspective	• Venipuncture is safe and standardized • Minimal time and effort requirement	• Requires patient education on how to collect a 24-hour urine collection adequately without over- or under-collecting • Requires patient effort and is usually inconvenient
Technical—protocol and interpretation	• Given aldosterone variability, requires a liberalized approach for interpretation (see Figure 4a) • Does not require any dietary preparation	• Requires that patient be on a relatively high-sodium balance for interpretation (see Figure 4b) • Requires measurement of urinary sodium and creatinine to ensure adequate urine collection and appropriate sodium balance • May require dietary sodium loading protocol to ensure a high-sodium balance, which adds additional effort, inconvenience, and potential risk for worsening hypertension and/or hypokalemia
Technical—laboratory	• Plasma preparation is standard • Immunoassay and LC–MS/MS techniques protocolized at laboratories where available	• Urine requires acidification prior to measurement • Following acidification, immunoassay and LC–MS/MS techniques protocolized at laboratories where available
Cost	• Variable depending on location and assay type • Cost of single plasma aldosterone measurement (in addition to renin)	• Variable depending on location and assay type • Cost of urinary acidification, urine free aldosterone, urine sodium, and urine creatinine • Generally, more expensive than a spot plasma aldosterone

Abbreviations: LC–MS, liquid chromatography–tandem mass spectrometry; PA, primary aldosteronism.

tests have been proposed[179–181,184,190] though are not yet incorporated into clinical practice guidelines.

Second, and related, aldosterone concentrations are not fixed but rather can vary substantially within an individual and across PA patients.[191–195] Like many other hormones, the production of aldosterone can exhibit marked variability. In a study of patients with overt PA, aldosterone values on different days varied by 31% and the ARR by 45%, with a third of PA patients having at least 1 aldosterone value below the conventional threshold of 10 ng/dl and a quarter having at least 1 ARR below 20 ng/dl per ng/ml/h.[195] This variability may be due to circulating factors and/or the variable expression of receptors for these factors in PA tissue.[70] Studies have shown that aldosterone-producing foci in PA may express variable degrees of MC2R, thereby rendering some degree of aldosterone production under the control of ACTH[57,62,64,66,68]; dysregulated aldosterone production in PA, along with 18-hybrid steroids indicative of dysregulated CYP11B2 expression, can be enhanced by ACTH and depressed with dexamethasone.[65,196,197] Further, variability in aldosterone production in PA may be induced by posture (angiotensin II modulation), variations in reproductive hormones (LH/GnRH), fasting or prandial status (GIP), vasopressin and serotonin activity, and procedural sedation or analgesia.[57,62,68,69,189,194,198–200]

Thus, *clinicians should not be dissuaded from the possibility of PA because the aldosterone concentration appears "too low."* The categorization of aldosterone levels as "low" or "high" is overly simplistic and misleading; rather, clinicians should analyze whether aldosterone production is "*physiologically appropriate vs. inappropriate*." In a high-risk patient with renin suppression, the clinician should assume "*PA until proven otherwise*" since virtually any aldosterone production in this context could represent the inappropriate and nonsuppressible pathophysiology that defines PA and enriches for response to MR antagonists.

Diagnosis and dynamic aldosterone suppression testing

Given the lack of an international, standardized, definition of PA, and the variable access to resources, time pressure on practicing clinicians, values of healthcare systems, and unique healthcare economics, we believe there is no single and uniform approach to diagnosing PA. Rather, there are multiple approaches that permit clinicians to use available resources, and their comfort level, to classify the patient appropriately. The most pragmatic approach relies on interpreting circulating measurements of renin and aldosterone. Although a single plasma aldosterone concentration may not reflect integrated daily aldosterone production, a liberalized approach to interpreting the results can provide a practical solution to this problem. Alternatively, specialists, and clinicians with more experience, can also consider using the results of 24-hour urinary aldosterone measurements to assess for PA (Figure 4). This approach involves more effort on the part of the clinician and patient, more sophisticated measurement techniques, and may require dietary and medication interventions; however, the results are generally more reliable and reflective of underlying physiology (Table 3).

In patients with a high clinical pretest probability, the presence of suppressed renin and an aldosterone concentration greater than 15 ng/dl (via any assay) is sufficient to clinch the diagnosis, especially if in the presence of hypokalemia, and further dynamic testing is not necessary.[177,201,202]

In high-risk populations who have a suppressed renin but an aldosterone concentration <5 ng/dl, particularly using an immunoassay, the possibility of PA is unlikely. If these results were accompanied by hypokalemia, they should be repeated following potassium supplementation since hypokalemia can substantially lower aldosterone production.[203] The exclusion of PA should not deter from the use of empiric MR antagonists as they have been shown to be effective at lowering blood pressure in low-renin hypertension, possibly via mechanisms independent of aldosterone.[204,205] Alternatively, the lack of renin suppression in the absence of medications known to raise renin in PA makes the possibility of PA unlikely (though there are rare instances when PA does present with a nonsuppressed renin yet a very high ARR).

For all remaining instances, that is a high-risk patient with renin suppression and an aldosterone concentration between 5 and 15 ng/dl, clinicians should assume "*PA until proven otherwise*" (Figure 4a). Empiric MR antagonist therapy can be considered in those who prefer not to pursue surgery or in whom unilateral PA is unlikely. Dynamic aldosterone suppression testing can be considered if there are any doubts regarding the diagnosis or if increased confidence is desired prior to localization or surgery. These dynamic tests are often referred to as "confirmatory" tests; however, we prefer to regard their value as "*exclusionary tests*" since the diagnostic mindset should already be "*PA until proven otherwise*." Further, there are multiple unvalidated aldosterone suppression testing protocols, each with their own relatively arbitrary thresholds; reliance on this type of testing can erroneously exclude participants who are likely to benefit from targeted therapies for PA.[51,172,206,207] The complete suppression of aldosterone production using an aldosterone suppression test (such as oral or intravenous sodium loading, or fludrocortisone or captopril challenge) implies physiologic aldosterone production and excludes PA; however, the abject failure, or even *marginal* failure, to inhibit aldosterone production suggests some shade of mild, moderate, or overt PA that is likely to respond to targeted therapy.[208]

An alternative to relying on plasma aldosterone concentrations is to measure 24-hour urinary aldosterone excretion rates (Figure 4b).[51,209,210] Since many patients in industrialized societies will already be in a relatively high dietary sodium state, urine collection without dietary modification may be sufficient; however, to ensure a high-sodium balance, it may be necessary to intervene with dietary sodium loading, which adds additional considerations to this methodology. When in a high-sodium balance, urine aldosterone values >10 mcg in high-risk individuals with suppressed renin likely confirms PA, whereas values between 6 and 10 mcg are strongly suggestive of PA pathophysiology,[51,162,209,210] and values <6 mcg likely exclude the possibility of PA.

We recognize that there are many approaches to diagnosing PA[164,208,209]; however, given the high prevalence and low detection rates of PA, we emphasize to the reader that virtually any aldosterone production in the setting of renin suppression in a high-risk patient population should be regarded as a phenotype of PA pathophysiology that, at minimum, warrants MR antagonist therapy.

CORTISOL COSECRETION IN PA

It has become increasingly evident that cortisol cosecretion is a relatively common occurrence in PA.[12,211–217] The prevalence of mild autonomous cortisol secretion (defined as a post-dexamethasone cortisol of ≥1.8 mcg/dl without overt clinical features of Cushing syndrome)[218,219] in PA has been reported to range from 4% to 27%[12,211–217,220–223]; however, prevalence estimates have been even higher when using more sensitive methods at detecting glucocorticoid excess.[142,212,216,224] The possibility of cortisol cosecretion in PA is generally restricted to patients who have a visible adrenal mass on cross-sectional imaging, as clinically relevant hypercortisolism usually requires a some degree of adrenocortical neoplasia. Therefore, all PA (and non-PA) patients with an adrenal mass should undergo dexamethasone suppression testing.

Cortisol cosecretion in PA has been associated with increased risk for adverse metabolic, vascular, kidney, and psychiatric outcomes.[12,212–215,224,225] In addition, PA patients with cortisol cosecretion have a high risk of developing secondary adrenal insufficiency following a curative unilateral adrenalectomy. In some studies, 30%–50% of PA patients developed postoperative adrenal insufficiency.[142,216,226] Although most patients were able to be weaned from glucocorticoid replacement over time,[217] some did require long-term glucocorticoid replacement.[216,217]

IMAGING AND LOCALIZATION

Cross-sectional imaging is recommended once PA is diagnosed to evaluate the rare possibility of adrenocortical carcinoma, and to provide an anatomical map prior to AVS or surgery. Computed tomography and magnetic resonance imaging can detect morphological abnormalities in the adrenal glands; however, *they cannot differentiate aldosterone-producing foci from common and incidental nonfunctional adrenal masses, nor can they detect APMs within otherwise morphologically normal-appearing adrenal glands*. The discrepancy between cross-sectional imaging and functional histopathology has been well documented in many studies; more than half of morphologically normal-appearing adrenal glands may be a source of aldosteronism in PA when assessed by AVS.[227] Despite the heterogeneity in AVS protocols,[228–230] the discordance rates between imaging findings and AVS has been consistently reported to be at least 20%–55%.[229–235]

AVS remains the best method to differentiate unilateral from bilateral PA. Some consensus statements have suggested that young patients with florid PA and a unilateral adrenal mass may forego AVS and proceed directly to surgical adrenalectomy[162,236,237]; however, recent studies have suggested that this assumption may not be correct in a sizeable proportion of patients.[227,238–240]

Table 4. Variations in adrenal venous sampling protocols that could affect results and interpretations

	Advantages	Disadvantages
Catheterization method		
Sequential	Technically simpler	Could result in factitious lateralization, particularly when the time between 2 samplings is more than 15 minutes
Simultaneous	Helps minimize the difference due to sampling times between adrenal glands	Technically more involved
Sampling		
Single adrenal venous sample	More convenient and less cost compared with multiple samples	Lacks precision and can result in misinterpretations owing to variability in aldosterone production
Multiple adrenal venous samples	Improves precision during AVS when calculating A/C ratio	Requires additional cost and time
Cosyntropin use	Enhances the selectivity index to increase confidence in successful adrenal vein cannulation Decreases the variability of aldosterone	Can lower lateralization index and lateralization rates, leading to discordant interpretations, and may result in fewer patients diagnosed with lateralizing PA. Therefore, unstimulated data provide more reliable interpretations for lateralization
Confirmation of catheter placement		
Cone-beam CT	Improves AVS success rate by confirming accurate catheterization, particularly to the right adrenal vein May reduce total radiation exposure during AVS	Image degradation caused by several artifacts due to breath-hold or posture (patients are required to raise their arms above the head) Not available in all centers
Rapid intraprocedural cortisol assay	Improves AVS success rate by allowing biochemical confirmation of accurate catheterization during the procedure May reduce total radiation exposure during AVS	May increase the procedural time (depending on the turnaround time for each laboratory) Not available at all centers and not validated
Standard cortisol assay	Available at nearly all AVS centers No additional cost	Slow turnaround time

Abbreviations: A/C, aldosterone-to-cortisol ratio; AVS, adrenal venous sampling; CT, computed tomography; PA, primary aldosteronism.

AVS results are more reliable and reproducible when performed by experienced interventional radiologists at high-volume centers.[241] However, AVS is a highly technical and operator-dependent procedure, with protocols that vary from institution to institution.[228] The main differences in AVS protocols that may affect results and interpretations are summarized in Table 4.[189,228,242–250] More stringent criteria to determine lateralization can increase the proportion of missed patients with unilateral PA who may benefit from adrenalectomy.[227,234,251] There has also been some concern that cortisol cosecretion may interfere with AVS interpretations,[217,252,253] namely misclassifying some patients who may have benefited from a curative unilateral adrenalectomy as having bilateral disease. Future studies to determine the precise impact of cortisol cosecretion on AVS interpretations are needed.

In the only randomized controlled trial to assess the value of AVS, when compared with cross-sectional imaging, the SPARTACUS trial found no short-term differences in blood pressure control between medical and surgical therapy.[254] However, there were a number of critiques of this study, including its short duration, risk for potentially misclassifying PA patients who may have been eligible for curative adrenalectomy, and use of ACTH infusions during AVS (Table 4).[255] Subsequently, several studies have shown that AVS-guided surgical treatment resulted in better clinical outcomes and more complete biochemical success than imaging-guided treatment alone, affirming the value of AVS, when available, as the most reliable method to differentiate between unilateral and bilateral PA.[233,256]

TREATMENT

The general approach to treating PA depends upon whether the aldosteronism is unilateral, and therefore amenable to a curative intervention, or bilateral, and therefore more amenable to chronic medical therapy. As discussed in the *Pathogenesis of PA*, the vast majority of PA is likely to be caused by diffuse and heterogeneous processes that occur bilaterally in the adrenal glands, whereas a minority is likely to represent entirely unilateral disease amenable to cure, particularly in younger individuals. Treatment of familial forms of PA is discussed elsewhere.[257]

Lateralizing PA

For patients with lateralizing PA who are healthy enough and willing to undergo surgery, adrenalectomy to cure (or substantially improve) PA is the treatment of choice.[162] Adrenalectomy is now primarily performed via a laparoscopic or retroperitoneoscopic approach.[258–261] Routinely, complete adrenalectomy should be performed as generally AVS is limited to determining the side of aldosterone secretion, but not whether a specific adrenal nodule is the source of aldosterone excess.[162] Where available, segmental sampling during AVS may allow the surgeon to undertake partial

adrenalectomy. Importantly, even when AVS indicates strong lateralization that benefits from adrenalectomy, there may still be residual or emergent PA from the contralateral gland (owing to APM/APN); while some forms of lateralizing PA represent truly unilateral disease, grossly asymmetric bilateral disease is common.[262]

Specific criteria for biochemical and clinical success following adrenalectomy have been set forth by the multinational Primary Aldosteronism Surgery Outcomes (PASO) study.[263] Complete biochemical success is defined as normalization of the ARR, along with resolution of potential hypokalemia, and is achieved in the vast majority of cases including in 94% of patients in the PASO study.[110,263–271] PASO characterized clinical success based upon blood pressure control, with complete clinical success defined by normalization of blood pressure without any antihypertensive medications, and partial clinical success defined by a reduction in the number of antihypertensive medications required or a reduction in blood pressure with the same number of antihypertensive medications.[263] The PASO study demonstrated that 37% of patients achieved complete clinical success while an additional 47% of patients achieved partial clinical success[263]; similar results have been demonstrated in other studies.[256,264,266,267,272–276]

A common question that arises in the treatment of lateralizing PA is whether surgical adrenalectomy improves long-term outcomes beyond medical therapy alone. No randomized trials have answered this directly, largely due to a perceived lack of clinical equipoise. It should be noted that the observational studies that have compared surgical (almost exclusively lateralizing PA) vs. medical (primarily bilateral PA or PA with unconfirmed lateralization) therapy are confounded by inherent differences in the clinical presentation and underlying pathophysiology and severity between unilateral and bilateral PA. Nonetheless, observational studies that have attempted to control for these differences have demonstrated that adrenalectomy in unilateral PA significantly reduced the risk for cardiovascular events,[124,125,131,277] kidney disease,[135,278,279] type 2 diabetes mellitus,[125,280] and mortality[126,278] while improving quality of life[271,281–283] compared with medical therapy. One large cohort study demonstrated that not only was adrenalectomy for patients with unilateral PA associated with lower all-cause mortality compared with essential hypertension patients, but also that adrenalectomy had a beneficial effect over MR antagonist therapy on mortality and cardiovascular events in lateralizing PA.[284]

Some centers have used ablative procedures in the treatment of unilateral APA. While concerns have been raised in regard to how ablation compares to surgical adrenalectomy given the lack of histopathology provided and the potential for leaving behind residual adrenal cortical tissue, a number of studies have suggested that ablation is safe and effective.[285–289] One randomized controlled trial comparing ablation vs. medical therapy in the treatment of unilateral PA demonstrated that 81% of patients treated with ablation achieved complete or partial hypertension remission along with improvement in biochemical parameters.[287] Future clinical trials of ablation vs. adrenalectomy are needed to compare their clinical and cost effectiveness and further define patient populations that are likely to benefit from each approach.

Bilateral PA

For patients with bilateral PA, or those with unilateral PA who do not undergo adrenalectomy, dietary sodium restriction and chronic MR antagonist therapy are the recommended treatments.[162] Effective dietary sodium restriction can result in volume contraction, a rise in renin, and normalization of blood pressure and ARR, in patients with PA.[79] However, sustaining this degree of sodium restriction (often <1,500 mg per day) can be challenging; therefore, combined therapy with MR antagonists is usually necessary.

The 2 most commonly prescribed MR antagonists are spironolactone and eplerenone. Spironolactone is more potent, longer acting, and generally less expensive than eplerenone. However, antiandrogenic effects (including gynecomastia, decreased libido, and menstrual irregularities) at higher and sustained doses can be limiting. In the future, newer generation nonsteroidal MR antagonists may expand the therapeutic options available for PA patients.[290–292] When MR antagonists are not tolerated or sufficient, epithelial sodium channel inhibitors, such as amiloride, are also effective options to lower blood pressure and normalize potassium.[80,293,294]

A common question that arises is "what is the goal of medical therapy in PA?" Historically, MR antagonists have been titrated to target normalization of blood pressure and serum potassium. However, recent data from at least 4 studies have shed more insights into pathophysiology-based approaches to treatment. Cohort studies have shown that PA patients treated with MR antagonists have a significantly higher risk for adverse cardiovascular events, atrial fibrillation, chronic kidney disease, and death, when compared with those with essential hypertension, despite achieving similar blood pressure control.[124,125,135] In an American cohort, this excess risk was predominantly driven by PA patients whose renin remained suppressed despite MR antagonist therapy; in contrast, when MR antagonist therapy in PA resulted in substantial increases in renin, the excess risk was mitigated.[124,125] Another large prospective study from Taiwan that evaluated patients with unilateral PA treated with MR antagonists, demonstrated similar findings, wherein a persistently suppressed renin was associated with a higher risk of major adverse cardiovascular events and death compared with those whose renin increased.[284] Similarly, a German study reported a greater reduction in left ventricular hypertrophy among PA patients who achieved unsuppressed renin levels with MR antagonists compared with those whose renin levels remained suppressed.[277] Collectively, these studies suggest that in addition to targeting normalization of blood pressure and serum potassium, clinicians should also consider targeting a rise in renin with MR antagonist therapy as a method to ensure optimized long-term risk reduction. A rise in renin will often require more aggressive MR antagonist dosing and reflects MR blockade sufficient enough to induce a level of volume contraction. With more aggressive MR antagonist dosing, other antihypertensive medications can be reduced or consolidated, and closer monitoring is

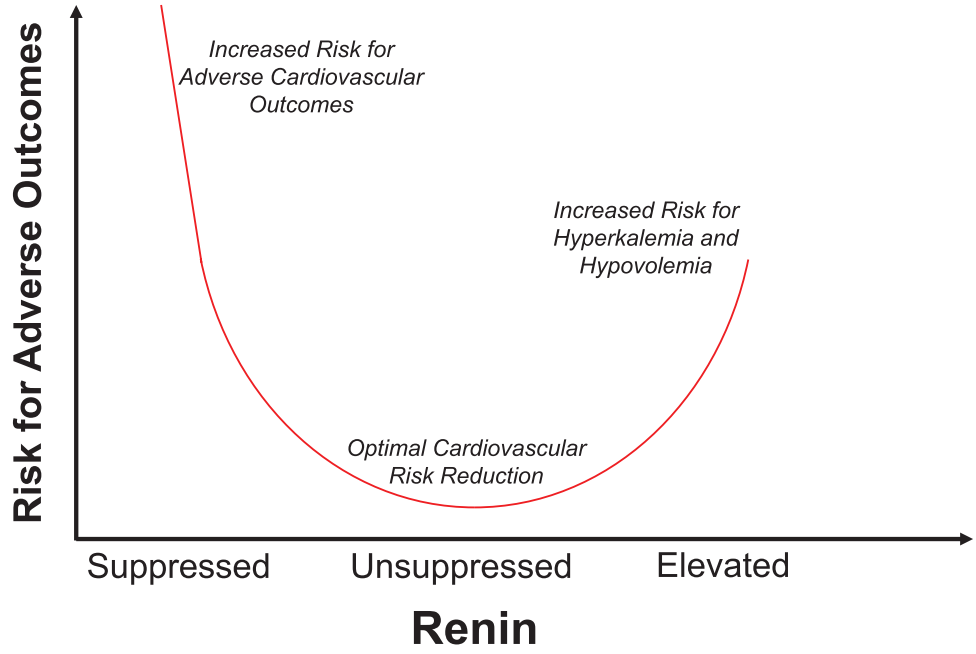

Figure 5. Targeting renin levels during mineralocorticoid receptor antagonist therapy. The primary objectives of MR antagonist therapy include normalization of blood pressure and potassium. Once these objectives are achieved, a rise in renin is a biomarker that is associated with lower risk for adverse cardiovascular outcomes. An unsuppressed renin activity, 1.0–2.0 ng/ml/h, is an ideal range to target; however, it is likely that any increase in renin from its baseline suppressed state is indicative of beneficial MR blockade. Excessive uptitration of MR antagonists associated with much higher renin levels may herald increased risk for hyperkalemia and/or relative hypovolemia and renal hypoperfusion. Abbreviation: MR, mineralocorticoid receptor.

required to avoid adverse effects such as antiandrogenic and progestational, as well as hyperkalemia and hypovolemia, particularly among patients with chronic kidney disease (Figure 5). Hyperkalemia in chronic kidney disease can now be managed with the use of novel potassium binders and with SGLT2 inhibitors.[295,296]

One remaining area of uncertainty in regard to the treatment of bilateral PA is whether unilateral adrenalectomy should be considered in certain cases where clinical optimization with MR antagonists cannot be achieved. In this scenario, unilateral adrenalectomy to attenuate disease severity, rather than biochemical cure, can be considered. Several case series and personal experiences have shown that noncurative unilateral adrenalectomy can be an effective and safe option to improve biochemical and clinical sequelae associated with bilateral PA.[297–299]

FUTURE DIRECTIONS

The next 5–10 years are likely to see emerging research focused on noninvasive methods to localize the source of PA as well as novel methods to treat PA. However, a key public health priority must include raising awareness for PA, increasing screening rates, and increasing the use of MR antagonists.

Newer imaging modalities and biomarkers have been investigated as a potential tool to aid subtype differentiation in PA. NP59 scans, although having low sensitivity in detecting lateralizing PA, can be used when AVS is unavailable or inconclusive.[236,237] ^{11}C-Metomidate positron emission tomography has shown some promise in subtype differentiation[300,301]; however, the concordance with AVS results is still not ideal.[302] Adrenal steroid profiling is another promising approach to differentiate idiopathic hypertension from PA, and lateralizing from bilateral PA.[303–305] Finally, many prediction models have been developed to predict subtype differentiation noninvasively, though they still lack reproducibility and external validation.[306–308]

Novel nonsteroidal MR antagonists have been shown to be safe and effective at lowering blood pressure in PA,[309] and capable of lowering risk for cardiovascular and kidney disease progression in patients with chronic kidney disease[290–292]; whether they may provide long-term and durable risk reduction in PA remains to be seen. In addition, several phase II studies evaluating novel aldosterone synthase inhibitors are currently underway; the possibility of targeted CYP11B2 inhibition could be a game-changer for the treatment of PA and other aldosterone-driven conditions.

We hope new guidelines will bring together multiple medical societies to sound the alarm on the high prevalence and unrecognized nature of PA. Novel educational approaches to raise awareness and simplify the pathway to diagnosis or empiric treatment for PA (as suggested herein) are much needed.

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