Evaluation and Management of Primary Aldosteronism

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KEYWORDS

• Primary aldosteronism • Hypertension • Cardiovascular risk

KEY POINTS

- Primary aldosteronism is increasingly recognized as a common cause of hypertension and cardiovascular disease.
- Updated guidelines recommend universal screening for all patients with hypertension, using a low renin and inappropriately elevated aldosterone and moving away from aldosterone suppression tests.
- New treatments such as adrenal ablation, nonsteroidal mineralocorticoid receptor antagonists, and aldosterone synthase inhibitors are emerging as promising additions and alternatives in the treatment of primary aldosteronism.

INTRODUCTION

Once considered a rare endocrine disorder characterized by the classic Conn's tumor, primary aldosteronism (PA) is now recognized as a common yet underdiagnosed cause of hypertension.[1–5] Indeed, renin-independent aldosterone production, the hormonal signature of PA, can be found in up to 30% to 40% of individuals with hypertension, with overt forms of PA in up to 25% of those with resistant or uncontrolled hypertension.[1,6–9] Given that hypertension remains the leading modifiable risk factor for cardiovascular morbidity and mortality, PA has become a major public-health concern, especially since targeted treatments can mitigate much of this excess risk.[10–14]

Recent evidence indicates that PA exists along a spectrum rather than as a dichotomous disease.[1,15] This shift in thinking was driven by advances in immunohistochemistry for aldosterone synthase (cytochrome P450 family 11 subfamily B member 2 [CYP11B2]) leading to the identification of aldosterone-producing micronodules throughout morphologically normal adrenal cortex,[16–19] the identification of approximately a dozen pathogenic somatic mutations that cause PA and

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Abbreviations	
APAs	aldosterone-producing adenoma
ARR	aldosterone-to-renin ratio
ASIs	aldosterone synthase inhibitors
AVS	adrenal vein sampling
CKD	chronic kidney disease
CT	computed tomography
ENaC	epithelial sodium channel
MR	mineralocorticoid receptor
MRAs	mineralocorticoid receptor antagonists
OSA	obstructive sleep apnea
PA	primary aldosteronism
SST	saline suppression test

frequently arise within aldosterone-producing micronodules,[19,20] but also by the recognition that no single biochemical threshold can dichotomize PA from non-PA.[1,15,21,22] The continuum of renin-independent aldosterone production can also be identified in normotensive people,[1,6,15,23–25] as can aldosterone-producing adrenal micronodules,[19] and this pathophysiology has been shown to correlate with the development of incident hypertension, adverse cardiac remodeling, and cardiovascular outcomes.[7,25,26]

Herein, we comprehensively review the latest updates in the evaluation and management of PA.

CLINICAL SPECTRUM OF PRIMARY ALDOSTERONISM

Prevalence of Primary Aldosteronism

The prevalence of PA varies markedly across patient populations. Reported rates range from 6% to 14% among unselected patients with hypertension in primary care,[27,28] to over 20% in referral centers, with rates varying widely across studies.[29,30] Certain subgroups report even higher prevalences including in resistant hypertension (11%–29%),[1,31,32] hypertension with hypokalemia (nearly 30%),[33] and hypertension with atrial fibrillation (42%).[34] Since there is no universal definition of PA, prevalence estimates rely heavily on the relatively arbitrary definition used and the degree of bias in the population surveyed. When investigating prevalence by identifying renin-independent aldosterone production, the fundamental biochemical signature of PA, prevalence estimates in people with hypertension can range into the 25% to 40% range.[1,31,32,34] For example, in the recent BaxHTN clinical trial that sought to evaluate the efficacy of the aldosterone synthase inhibitor baxdrostat in people with uncontrolled or resistant hypertension, at minimum 25% of individuals met international criteria for PA whereas up to 40% may have likely had some degree of PA pathophysiology.[8]

Clinical Characteristics of Primary Aldosteronism

Patients with PA tend to exhibit higher blood pressure and more frequent features of the metabolic syndrome, including greater waist circumference, lower HDL cholesterol, higher fasting glucose and triglycerides, than individuals with non-PA hypertension.[27]

They have also been shown to have a higher risk of adverse cardiovascular events and target organ damage compared to those with essential hypertension, independent of blood pressure levels.[35,36] Patients with PA have a higher risk of developing chronic kidney disease (CKD) and CKD progression when compared to those with essential hypertension, independent of blood pressure.[37–39]

Hypokalemia occurs in 9% to 37% of patients with PA, with a higher prevalence observed in those with aldosterone-producing adenoma (APAs).[40] Severe hypokalemia is less common but is strongly suggestive of PA.[33] It is important to underscore that most patients with PA do not have hypokalemia, thus the presence of hypokalemia may dramatically increase the pretest probability for PA, but the absence of hypokalemia should not influence the suspicion.

Obstructive sleep apnea (OSA) is highly prevalent in individuals with PA, affecting more than 50% of afflicted patients.[41] These 2 diseases share overlapping pathophysiological mechanisms.[42] Excess aldosterone causes fluid retention that can shift to the neck and promote apnea. In turn, hypoxia in OSA activates the renin-angiotensin-aldosterone system, leading to aldosterone increase through renin-dependent mechanisms. Obesity amplifies this interaction by promoting both airway obstruction and aldosterone overproduction.[42]

DIAGNOSIS

There are many approaches to diagnosing PA. The Endocrine Society guidelines have traditionally been the source of the most adopted and widely accepted approach. Updates to these guidelines were published in 2016 and most recently in 2025. The principal differences between the 2016 and 2025 Endocrine Society guidelines for the diagnosis workflow of PA are summarized in **Table 1**.

Screening Recommendations for Primary Aldosteronism

The Endocrine Society, European Society of Cardiology, and Endocrine Society of Japan recommend screening all patients with hypertension for PA,[12,43,44] whereas the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for high blood pressure recommend screening for PA in patients with resistant hypertension regardless of whether hypokalemia is present.[45]

The 2025 Endocrine Society Guidelines on PA[43] recommend screening be performed by measuring serum/plasma aldosterone concentration and either direct renin concentration or plasma renin activity. Serum potassium should be measured at the same time to help with interpretation. The objective of the screening test is to identify renin-independent aldosterone production, characterized by a low renin and inappropriately elevated aldosterone levels. Most patients with PA have a low renin as defined by a renin activity of less than 1 ng/mL/h or direct renin concentration of less than 8.2 mU/L.[43] Although any plasma aldosterone concentration in the context of a low renin may indicate PA pathophysiology amenable to aldosterone-directed therapy, a plasma aldosterone greater than 10 ng/dL when measured via immunoassay, or greater than 7.5 ng/dL when measured via liquid chromotography tandem mass spectroscopy (LC-MS/MS), indicates PA.[43] The aldosterone-to-renin ratio (ARR) was once the cornerstone of PA screening.[46] However, the updated diagnostic framework de-emphasizes reliance on ARR alone and encourages individual evaluation of aldosterone and renin levels, providing a more physiologic assessment of renin-independent aldosteronism.[43] Medication withdrawal can be performed if feasible, however, modern practice encourages testing without changing medications to simplify the evaluation.[43] Most antihypertensives (diuretics, mineralocorticoid receptor antagonists [MRAs], angiotensin converting enzyme [ACE] inhibitors, and angiotensin receptor blockers) tend to stimulate renin, thus leading to false-negative results on screening. Detecting suppressed renin-independent aldosteronism despite these therapies provides particularly strong evidence for PA. If renin levels are not low, or aldosterone levels are not sufficiently high, then targeted medication washouts can be conducted before repeating testing.

Table 1
Main differences between the 2016 and 2025 endocrine society guidelines for diagnosis of primary aldosteronism

	2016 Endocrine Society Guideline	2025 Endocrine Society Guideline
Prevalence statement	>5% and possibly >10% of patients with hypertension	5%–14% of individuals with hypertension seen in primary care and up to 30% in referral centers
Screening indications	*High-risk groups only*: resistant or severe hypertension, hypertension with hypokalemia, adrenal incidentaloma, sleep apnea, early onset hypertension, or a family history of premature cerebrovascular disease or PA	*All patients with hypertension*: interpreted based on local resources, expertise, and health care system capacity
Screening test	Morning, seated, ad lib diet: *Elevated ARR*	Morning, seated, ad lib diet: *Suppressed renin with inappropriately elevated aldosterone and an elevated ARR*. Diagnostic thresholds depend on immunoassay vs LC-MS/MS
Medication management during testing	*Stepwise medication withdrawa*l: stop MRAs, ENaC inhibitors, and potassium-wasting diuretics for $\geq$4 wk. Withdraw other interfering agents (beta-blockers, ACEi/ARB, and CCBs) for $\geq$2 wk if initial screen is nondiagnostic and BP can be controlled with noninterfering agents	*Pragmatic medication withdrawal*: Allow minimal (MRA and ENaC) or no withdrawal, interpret results in context and repeat testing if suspicion remains high
Aldosterone suppression testing	*Required after positive ARR*: saline infusion, oral sodium loading, fludrocortisone suppression, or captopril challenge. Exception: hypokalemia, suppressed renin, and PAC >20 ng/dL	Aldosterone suppression not necessary for diagnosis. Aldosterone suppression testing can be considered in situations where screening results suggest an intermediate probability for lateralizing PA to help determine the utility of adrenal venous sampling

Abbreviations: ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blockder.

Diagnostic Algorithm for Primary Aldosteronism

We have proposed a streamlined algorithm (**Fig. 1**) where all people with hypertension are screened for PA using renin, aldosterone, and potassium levels, where a suppressed renin level in conjunction with an inappropriately elevated aldosterone is diagnostic for PA.[47,48] If this biochemical pattern is not observed and clinical suspicion is high, clinicians should consider potential false-negative results due to factors such as interfering medications or hypokalemia. Once the diagnosis is established, patients are assessed for their interest and eligibility for adrenalectomy. For surgical candidates, adrenal vein sampling (AVS) should be performed if widely available. Those

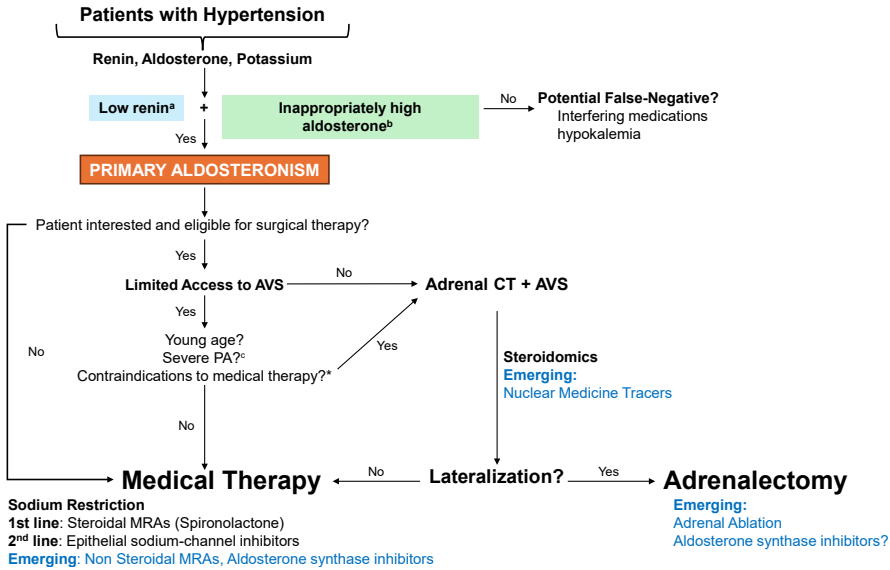

Fig. 1. Simplified evaluation algorithm for PA. Made using MS PowerPoint. Recent guidelines recommend screening all individuals with hypertension using renin, aldosterone, and potassium measurements, without withdrawal of antihypertensive medications. A low renin with inappropriately elevated aldosterone supports the diagnosis of PA. When renin is not low, possible false-negative results should prompt correction of hypokalemia or review of interfering medications. In this proposed algorithm, decisions following a PA diagnosis are guided by patients' local resource availability and probability of lateralization. In settings with limited access to AVS, localization efforts should be prioritized for younger patients, those with severe disease, and/or contraindications to medical therapy. Others may proceed directly to empiric MRA therapy. [a]Low renin: renin activity of less than 1 ng/mL/h or direct renin concentration of less than 8.2 mU/L. [b]Inappropriately high aldosterone: plasma aldosterone greater than 10 ng/dL (277 pmol/L) when measured via immunoassay, or greater than 7.5 ng/dL (208 pmol/L) when measured via LC-MS/MS. [c]Severe PA: hypokalemia, direct renin concentration less than 2 mU/L or plasma renin activity less than 0.2 ng/mL/h and plasma aldosterone concentration ~20 ng/dL (~554 pmol/L) by immunoassay or greater than ~15 ng/dL (~416 pmol/L) by LC-MS/MS. [c]Contraindications to MRA: severe renal impairment, hyperkalemia, and hypotension. AVS, adrenal vein sampling; MRA, mineralocorticoid receptor antagonist.

who are younger, or have more severe PA, have a higher likelihood of benefiting from surgery, and thus should be prioritized for AVS when these resources are not easily available. The vast majority of patients will have nonlateralizing or bilateral PA, and/or will not be interested in a surgical procedure, and/or will be evaluated at locations that do not have access to high-quality AVS. For all of these instances, medical therapy should be pursued.

This resource-conscious algorithm broadens and simplifies screening in order to cast a wider net for detecting PA, enabling earlier intervention and reducing the long-term cardiovascular burden in the hypertensive population.

Aldosterone Suppression Testing

The use of aldosterone suppression tests for the diagnosis of PA has been shown to lead to inaccuracies.[21,49–53] In a 2022 systematic review and meta-analysis, Leung and colleagues[52] found that the evidence supporting confirmatory tests for PA

diagnosis was of very low quality, with considerable variability and high risk of bias, indicating that their routine use may miss true cases and should be reconsidered. These conclusions were confirmed in a prospective, blinded, diagnostic accuracy study where the seated saline suppression test (SST) failed to distinguish patients with PA who responded to PA-specific treatment from those who did not, with overlapping post-SST aldosterone values between responders and nonresponders.[49] The investigators concluded that the SST had poor diagnostic performance and a high false-negative rate, suggesting that reliance on this test may lead to missed diagnoses of PA.[49]

In the most recent guidelines, aldosterone suppression tests are no longer recommended for diagnosing PA, but rather as a tool to potentially help predict the likelihood of lateralizing disease, which could be confirmed with AVS.[43] However, some studies have shown that aldosterone suppression tests have poor accuracy at predicting lateralization outcomes.[50,54]

Tools for Subtyping Primary Aldosteronism

Profiling adrenal steroids such as 18-hydroxycortisol and 18-oxocortisol using mass spectrometry have been proposed as a tool to guide PA subtyping.[55–57] However, overlap between unilateral and bilateral disease, along with genotype-specific steroidomic signatures, limited availability, cost, and lack of standardization, restrict their widespread clinical application.[58]

New breakthroughs in nuclear medicine imaging are promising avenues to overcome the obstacle of PA subtyping, which currently relies on AVS, a technical and not widely available procedure.[59] Dexamethasone-suppressed ^{11}C-metomidate PET-computed tomography (CT) has shown to be noninferior to AVS for lateralization of PA.[60,61] ^{68}Ga-pentixafor PET-CT, a tracer targeting CXCR4, has shown high concordance with AVS and a correlation with CYP11B2 expression.[62,63] Its sensitivity decreases in nodules smaller than 1 cm.[62] While CXCR4 is overexpressed in APAs, some variability and overlap with nonfunctioning adrenal adenomas have been noted.[64] [18F] AldoView is a selective PET tracer for CYP11B2.[65] In the first human study of [18F] AldoView PET imaging, patients with unilateral APAs or aldosterone producing nodules had a positive [18F] AldoView PET, with uptake being associated to CYP11B2 expression.[66]

MANAGEMENT

Nonpharmacological Approaches to Primary Aldosteronism Management

Reducing dietary sodium intake is a well-established recommendation in the management in all types of hypertension.[45] In PA, sodium is the substrate that fuels the pathophysiology. Strict reduction of dietary sodium intake in PA has been shown to lower blood pressure, raise renin, and reduce the ARR similar to the effect of pharmacologic MRA therapy.[67] Moreover, the magnitude of dietary salt intake appears to influence adverse cardiac remodeling in PA, as higher sodium intake correlated with greater left ventricular hypertrophy and reductions in salt intake after treatment was associated with a more important regression of cardiac mass and pulse pressure.[68–70]

Surgical and Interventional Approaches to Primary Aldosteronism Management

Surgical

Laparoscopic unilateral total adrenalectomy is the standard surgical treatment of patients with lateralizing PA who elect a surgical approach.[43]

Recent systematic review and meta-analysis have suggested that targeted medical therapy may be less effective than adrenalectomy.[14,71] Patients on MRAs had higher

blood pressure, required more antihypertensive agents at higher doses and experienced more adverse outcomes (including stroke, heart failure, and all-cause mortality) compared with those undergoing surgery.[14,71] However, these studies need to be interpreted in the context of limitations including suboptimal MRA dosing and adherence, differences in severity of the disease between groups and selection biases in who was offered adrenalectomy.[14,71] Surgery is also associated with greater regression of left ventricular mass and a lower risk of persistent hypertrophy compared with medical therapy.[72]

Interventional

Adrenal ablation has emerged as a minimally invasive alternative for treating PA in patients unsuitable for surgery, including CT-guided percutaneous radiofrequency ablation, endoscopic ultrasound-guided radiofrequency ablation, and catheter-based adrenal artery ablation.[73–79] In a recent meta-analysis including over 10,000 patients, adrenalectomy, percutaneous adrenal ablation (including radiofrequency, catheter-based chemical ablation, and embolization) and MRA therapy were compared in the treatment of PA.[74] The outcomes included blood pressure reduction, serum potassium normalization, and ARR improvement. Adrenalectomy ranked highest across all outcomes, ablation ranked second and MRA therapy ranked lowest, suggesting that while adrenalectomy remains the most effective approach, ablation may offer a viable alternative when surgery is not feasible.[74] In a randomized, medication-controlled trial, catheter-based adrenal ablation was shown to produce greater blood pressure reductions at 1 month, compared with spironolactone therapy.[75] By 6 months, blood pressure improvements were similar between groups, but patients in the ablation group showed a greater decrease in the defined daily dose of antihypertensive medications and a marked reduction in plasma aldosterone levels.[75]

Pharmacologic Options in Primary Aldosteronism Management

The old: steroidal mineralocorticoid receptor antagonist and epithelial sodium-channel inhibitors

MRAs are the cornerstone of medical therapy in PA.[43] Choice of MRA should take into account cost, availability, and side effects. The Endocrine Society 2025 guidelines recommend spironolactone over other MRAs due to its low cost and widespread availability.[43] Spironolactone is effective in reducing blood pressure and normalizing potassium in patients with PA.[80,81] However, antiandrogen side effects including gynecomastia, erectile dysfunction, and menstrual irregularities may limit tolerability.[43] Eplerenone, another steroidal MRA, is more selective for the mineralocorticoid receptor (MR) and has little risk of antiandrogenic side effects, making it preferred for men who experience these effects with spironolactone.

When initiating and titrating of an MRA for PA, a stepwise approach is recommended.[43] Treatment typically starts with low-dose spironolactone (12.5–25 mg daily) or eplerenone (25 mg once or twice daily), adjusted based on blood pressure, comorbidities, and potassium. The main goal of therapy is blood pressure control, with normalization of potassium as a secondary target. A rise in renin levels can be used as a marker of effective MR blockade to help guide MRA dose titration.[43] Multiple observational studies have shown cardiovascular and renal benefits in targeting a rise in renin to guide MRA therapy.[36,82–87]

The risk of hyperkalemia during MRA therapy increases with older age (>65 years), CKD, and diabetes.[88] If hyperkalemia occurs, management strategies include adding a thiazide, loop diuretic, sodium-glucose transporter 2 (SGLT2) inhibitor, novel potassium binders, or stopping ACE inhibitors or angiotensin receptor blockers if applicable.[87,88]

Finally, epithelial sodium channel (ENaC) inhibitors (amiloride and triamterene) are recommended as an alternative when MRAs are not tolerated or available.[43] They have a blood pressure-lowering effect that appears to be equivalent to MRAs in patients with PA, but their impact on reducing MR-mediated organ damage remains unknown.[43]

The new: nonsteroidal mineralocorticoid receptor antagonists

Nonsteroidal MRAs, such as finerenone, are new agents that have shown cardiovascular and renal benefits in randomized controlled trials involving patients with diabetes and CKD or heart failure.[89–91] These agents have a much lower affinity for the androgen or progesterone receptors, resulting in a more favorable side-effect profile.[92] In PA, evidence remains limited.[93,94] In a small short-term clinical trial comparing spironolactone to finerenone, effects on blood pressure, potassium, and renin were comparable in patients with PA.[93] In a real-world study where patients with PA were switched from eplerenone to finerenone due to drug shortage, blood pressure control was maintained, but fewer patients achieved complete clinical and biochemical responses, possibly due to finerenone's pharmacokinetics.[94]

The emerging: aldosterone synthase inhibitors

Aldosterone synthase inhibitors (ASIs) are a new class of drugs that act by blocking CYP11B2, the enzyme responsible for aldosterone synthesis. By directly suppressing aldosterone formation, ASIs lower MR activity, decrease ENaC activation and promote natriuresis through reduced distal sodium reabsorption.[95]

A phase 2 randomized, placebo-controlled, dose-ranging trial of lorundrostat in patients with uncontrolled hypertension (Target-HTN), most of whom had suppressed renin and elevated aldosterone showed significant dose-dependent reductions in blood pressure.[96] In the phase 3, randomized clinical trial (Launch-HTN) of over 1000 adults with uncontrolled or treatment-resistant hypertension, lorundrostat significantly reduced systolic blood pressure.[97]

In phase 2 and phase 3 studies of baxdrostat in patients with resistant and uncontrolled hypertension, dose-dependent reductions in blood pressure were observed compared to placebo.[8,98] Notably, at least 25% of participants in this study had a biochemical signature of PA. In a phase 2a open-label study of patients with established PA, baxdrostat substantially reduced systolic blood pressure (25 mm Hg), aldosterone, and ARR, while correcting hypokalemia.[99]

The safety profiles of baxdrostat and lorundrostat were favorable, with the most important risks being hyperkalemia and mild reversible declines in estimated glomerular filtration rate.[8,97]

In theory, if ASIs can selectively and sustainably inhibit aldosterone synthesis, these drugs might one day offer an alternative treatment to lateralized PA as a "medical aldosterone-ectomy." Phase 3 trials are ongoing and these results will determine whether these novel agents will become available for clinical use in patients.

SUMMARY

In summary, PA is now recognized as a common cause of hypertension in which targeted therapy can substantially mitigate the excess cardiovascular and renal risk associated with aldosterone excess. New guidelines streamline diagnosis by recommending a pragmatic approach that centers around identifying renin-independent aldosterone production without excessive requirements for medication changes or dynamic testing. Steroidomics, functional nuclear imaging, along with emerging therapies including nonsteroidal MRAs and ASIs, may further redefine how PA is subtyped and treated.

CLINICS CARE POINTS

- All patients with hypertension should be screened for PA, given its high prevalence and cardiovascular risk, with a low renin and inappropriate aldosterone production being the main biochemical characteristics supporting the diagnosis.
- Biochemical screening can be performed without changing antihypertensive medications.
- Aldosterone suppression tests are no longer recommended in the diagnostic pathway as they lack diagnostic accuracy, particularly in excluding the possibility of the diagnosis.
- ASIs and noninvasive tools to subtype PA (nuclear imaging and steroidomics) may reshape both medical management and subtype classification of PA.

DISCLOSURE

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