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Practical insights in the care of patients with primary aldosteronism: navigating a rapidly evolving field

Abstract

This review is based on the 2025 Endocrine Society Clinical Practice Guidelines for the evaluation and management of patients with primary aldosteronism (PA), reflecting the collective expertise and contributions of investigators and clinicians worldwide who have advanced the field. We highlight practical insights to facilitate the diagnosis, evaluation, and management of patients with PA. Our goal is to bridge evidence-based recommendations developed by experts in the field with the realities of day-to-day clinical practice and to provide clinically relevant teaching points for endocrinologists, urologists, nephrologists, and all clinicians caring for patients with PA.

Keywords: primary aldosteronism, renin, aldosterone, plasma aldosterone concentration, plasma renin activity, direct renin concentration, adrenal venous sampling, mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, dexamethasone suppression test

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Introduction

Primary aldosteronism (PA) is a disorder of inappropriate aldosterone production with important cardiovascular and renal consequences.[1–5] PA encompasses a broad spectrum of phenotypic diversity rather than representing a single, uniform disorder.

Clinical presentations range from relatively mild or subclinical disease to overt autonomous aldosterone excess, with variability in biochemical profiles, imaging findings, genetic mechanisms, and clinical manifestations. Importantly, aldosterone excess exerts vascular-toxic and systemic effects that extend beyond blood pressure elevation, contributing to cardiovascular, cardiometabolic, and renal injury**,** underscoring PA as a systemic disorder rather than simply a cause of hypertension.[5,6] The Endocrine Society clinical practice guidelines explicitly shifted the paradigm away from only testing "high risk patients/resistant hypertension" to universal screening regardless of the severity of hypertension or the patient's potassium levels.[7]

The historical evolution of PA merits recognition, beginning with pioneering work that established the potential for mineralocorticoids to cause tissue injury. Hans Selye was among the first to describe the deleterious effects of deoxycorticosterone acetate (DOCA), a potent mineralocorticoid**,** providing early experimental evidence of mineralocorticoid-mediated tissue damage.[2] At that time, aldosterone had not yet been identified and was provisionally referred to as "electrocortin." Subsequent work by Simpson, Tait, and colleagues led to the identification and isolation of aldosterone.[3,4] In 1954, collaborative efforts involving Dr. Jerome Conn culminated in the first adrenal resection by Dr. William Baum that successfully cured a patient with hypertension and hypokalemia. Their observations established the role of an adrenal adenoma as the source of excess aldosterone**,** providing the foundation for recognition of PA as a potentially curable form of secondary hypertension.[5,6]

Clinical and biochemical features of PA: premature cardiovascular disease

Adverse cardiovascular and metabolic effects of mineralocorticoid excess have been recognized for decades.[7,8] Hypertension and hypokalemia are classic manifestations of aldosterone excess and remain important clinical clues to the diagnosis of primary aldosteronism (PA).[1] However, hypokalemia is not present in all patients with PA, and many patients have normal serum potassium concentrations.[1,7] Therefore, normokalemia should not dissuade clinicians from considering or pursuing the diagnosis of PA in patients with high blood pressure.

Biochemically, primary aldosteronism (PA) is characterized by renin-independent aldosterone production that is inappropriate for the patient's physiologic state, typically occurring in the absence of volume depletion.[1] In contrast to normal physiology, aldosterone secretion remains inappropriately elevated despite suppression of renin (hence, renin independent) and the consequent expansion of extracellular fluid volume.[7] This autonomous aldosterone production distinguishes PA from secondary aldosteronism, in which aldosterone secretion appropriately increases in response to renin activation.

To restate, the clinical importance of PA extends well beyond blood pressure elevation. Persistent aldosterone excess promotes cardiovascular, renal, and metabolic injury through activation of the mineralocorticoid receptor, contributing to myocardial fibrosis, vascular remodeling, atrial fibrillation, chronic kidney disease, stroke, and impaired quality of life.[1–7]

Biochemical Screening for Primary Aldosteronism(PA)

Based on the 2025 Endocrine Society Clinical Practice Guideline, screening for primary aldosteronism (PA) should include measurement of serum or plasma aldosterone concentration (PAC) together with plasma renin, measured either as plasma renin activity (PRA) or direct renin concentration (DRC), with calculation of the aldosterone-to-renin ratio (ARR).[7]

Measuring aldosterone

Immunoassay method uses antibodies to detect aldosterone.[9] It is considered a faster method although may demonstrate less analytical specificity because structurally related steroids or metabolites can contribute to assay interference, potentially resulting in higher measured aldosterone concentrations.[7]

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Liquid chromatography–tandem mass spectrometry (LC-MS/MS) provides greater analytical specificity because it separates and identifies aldosterone based on its chromatographic and mass-spectrometric characteristics. Although technically more demanding, LC-MS/MS generally provides more specific measurement of aldosterone and has become increasingly important when precise quantification is clinically relevant, particularly in patients with impaired renal function.[1,7,9]

Measuring renin

Plasma renin can be assessed either as plasma renin activity (PRA) or direct renin concentration (DRC). PRA is an enzymatic measure that reflects the rate of generation of angiotensin I from angiotensinogen and is reported as ng/mL/h. In contrast, DRC directly measures the concentration of renin in plasma and is typically reported in mU/L. These are different analytical measurements and should not be considered interchangeable without using assay-specific reference ranges and aldosterone-to-renin ratio (ARR) thresholds.[1,7]

The 2025 guideline emphasizes that aldosterone and renin thresholds are provided as guidance rather than absolute diagnostic boundaries.[7] Results should be interpreted in the context of the patient's pretest probability, serum potassium concentration; (it is important to correct hypokalemia when testing for aldosterone to avoid falsely low aldosterone levels), medications, kidney function, dietary sodium intake, posture, and other factors that may influence renin and aldosterone concentrations. Local laboratory assay-specific reference ranges should be considered whenever available.

Interpreting laboratory data

Serum or plasma potassium should be measured concurrently to aid in the interpretation of aldosterone levels, as hypokalemia may suppress aldosterone and result in a falsely low value. The screening generally requires both suppressed renin and an aldosterone concentration that is inappropriately high relative to the renin level. Specifically, PA is suggested when PRA is ≤1 ng/mL/h or DRC is ≤8.2 mU/L, together with an aldosterone concentration of ≥10 ng/dL when measured by immunoassay or ≥7.5 ng/dL when measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS).[7,9] The aldosterone/renin ratio should not be interpreted in isolation from its components of aldosterone and renin. The most commonly used threshold for ARR is greater than 30 (for PAC ng/dL and PRA ng/mL/h); however, the guidelines acknowledge that some authors support alternative thresholds of 20 or 40 (for PAC ng/dL and PRA ng/mL/h).[1,7]

These thresholds should be viewed as guidance rather than absolute diagnostic cut points, as aldosterone and renin concentrations are influenced by assay characteristics, medications, sodium intake, volume status, and other patient-specific factors. There are renin mediated cases of aldosteronism that should be considered if renin is not suppressed, and there is no need to calculate the ARR, for example in patients with renal artery stenosis. Another common trap is attempting to calculate a ratio when both aldosterone and renin are very low because there is no aldosterone excess. The differential diagnosis in patients with low renin and low aldosterone includes cortisol excess, hypertensive variants of congenital adrenal hyperplasia (11 hydroxylase and 17 hydroxylase deficiencies), apparent mineralocorticoid excess due to 11 beta dehydrogenase deficiency, excessive licorice intake, Liddle syndrome.[10]

When interpreting the results, we pay attention to the patient's current medications. The following medications will increase the renin: Angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACE-i), diuretics, and MRA. Medications that will lower the renin include non-steroidal anti-inflammatory drugs (NSAID), renin inhibitors, clonidine and beta blockers.

MRAs raise circulating aldosterone by compensatory activation of the renin-angiotensin-aldosterone system (RAAS) by competitively blocking the mineralocorticoid receptor. This is a pharmacodynamic effect, not a lab artifact. Therefore, it is preferable to check aldosterone and renin levels before starting mineralocorticoid receptor antagonists.[7]

Dexamethasone suppression test in patients with PA and adrenal nodules: baseline ACTH and 1 mg dexamethasone suppression testing

The 2025 Endocrine Society Clinical Practice Guidelines introduced an important recommendation for patients with primary aldosteronism (PA) and an adrenal nodule: a 1-mg overnight DST should be performed.[7] This recommendation complements the broader endocrine evaluation of patients with adrenal nodules incidentally discovered, for whom a 1-mg overnight DST is also recommended to assess autonomous cortisol secretion.

This is an important nuance. It is clinically meaningful to identify patients with concurrent cortisol excess because of important implications including cardiovascular and metabolic risk assessment, perioperative glucocorticoid management, interpretation of adrenal venous sampling in selected patients, and postoperative surveillance for adrenal insufficiency.

A serum cortisol concentration >1.8 µg/dL (50 nmol/L) following the 1-mg overnight DST suggests autonomous cortisol secretion and warrants appropriate clinical evaluation.[7] In patients with adrenal incidentally discovered adrenal nodules without overt Cushing syndrome, the contemporary adrenal incidentaloma guideline refers to this finding as mild autonomous cortisol secretion (MACS) and recommends confirming ACTH independency.[7]

Because the 1-mg overnight dexamethasone suppression test (DST) is interpreted based on the post-dexamethasone morning cortisol, a baseline cortisol is not required for its interpretation. However, obtaining a morning plasma ACTH (together with cortisol and DHEA-S) at the time of baseline sampling—before dexamethasone is taken—can provide a useful physiologic context. In a patient not receiving exogenous glucocorticoids, a low or suppressed morning ACTH supports ACTH-independent (adrenal) cortisol secretion and helps characterize the source and magnitude of cortisol excess should the DST prove abnormal.

This information is particularly relevant when an adrenal nodule is present, because autonomous adrenal cortisol secretion may coexist with primary aldosteronism (PA). Recognizing concurrent cortisol excess preoperatively is clinically important: current guidance recommends assessing cortisol production with a DST in individuals with PA and an adrenal adenoma, as unrecognized co-secretion can complicate interpretation of adrenal venous sampling and predisposes to postoperative glucocorticoid insufficiency.[7] Patients with mixed PA and hypercortisolism have accordingly been shown to require postoperative glucocorticoid replacement far more often than those with PA alone.[10] Capturing the baseline biochemical profile therefore helps establish the underlying physiology and may inform subsequent evaluation and perioperative planning.

Practically, patients with suspected PA and or more adrenal nodules are advised that this evaluation requires two separate laboratory visits. At our institution, at the first visit, morning baseline

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samples are obtained for aldosterone, renin, a metabolic panel, ACTH, cortisol, DHEA-S, and plasma metanephrines (and, when appropriate, 17-hydroxyprogesterone and estrone) are collected. The patient then takes 1 mg of dexamethasone that night (typically at 11 PM), and a second blood draw for cortisol is obtained at 8 AM the following morning.

Of note, it is fundamental to review the medication list including estrogen-containing oral contraceptives because these primarily confound the serum cortisol measurement through a protein-binding mechanism elevating the total circulating cortisol. Other medications to keep in mind are the cytochrome P450 3A4 (CYP3A4) enzyme inducers including drugs to treat epilepsy accelerating the clearance of dexamethasone. Potent enzymes inducers include carbamazepine, phenytoin, phenobarbital, primidone.[11,12]

Identifying surgically curable aldosterone excess: lateralization with Adrenal Venous Sampling (AVS)

Adrenal venous sampling (AVS) is the reference standard for determining the source of aldosterone excess in patients with biochemically confirmed primary aldosteronism (PA) and establishes whether aldosterone secretion is unilateral or bilateral. When aldosterone secretion lateralizes to one adrenal gland, with relative suppression of the contralateral gland compared to peripheral vein, surgical removal of the affected adrenal gland offers the potential for biochemical cure of PA.[13–15]

A subset of patients will experience complete resolution of PA-mediated hypertension, representing a clinical and biochemical cure, whereas others will achieve substantial improvement in blood pressure control with a reduction in blood pressure-lowering medications. Importantly, hypokalemia usually resolves following successful removal of the source of autonomous aldosterone secretion, reflecting restoration of appropriate aldosterone physiology.[13–15]

Eliminating the source of autonomous aldosterone excess reduces chronic mineralocorticoid receptor activation in extrarenal tissues, including the vasculature and myocardium, and thereby limiting aldosterone-mediated vascular remodeling, myocardial fibrosis, and other forms of target-organ injury. This distinction is clinically important because patients with PA experience a greater burden of cardiovascular morbidity than patients with primary hypertension of comparable severity, underscoring the importance of identifying and treating the underlying aldosterone excess rather than focusing solely on blood pressure reduction.[13–15]

A frequently raised question is whether AVS can be reliably done when the patient is on MRAs. This is clinically important consideration as MRA mediated blockade can elevate renin and thereby stimulate renin-dependent aldosterone secretion from the contralateral adrenal gland in unilateral PA and from both glands in bilateral disease – confounding lateralization. When the risks of changing medications outweigh the benefits, evidence suggests that AVS can still be performed particularly if the plasma renin activity (PRA) is below 0.6-1 ng/ml/h.[13–15]

AVS strategies vary across centers, reflecting differences in practice. Establishing a standardized protocol remains a widely sought goal.[13–15]

Surgical resection is associated with lower all-cause mortality and fewer major adverse cardiovascular events than medical therapy, though this evidence is observational.[16,17]

Clinical predictors of surgical cure

The duration of hypertension and number of antihypertensive medications to lower blood pressure are among the most consistently reproducible predictors of cure. In addition, younger age, women, lower BMI, lower serum potassium are all variables associated with higher cure rate.[17–20]

Removal of the source of aldosterone excess does not necessarily erase years of established hypertension.

Long-standing hypertension may result in vascular remodeling and nephron injury that persists even after the aldosterone excess has been eliminated.

Importantly, biochemical remission does not necessarily equate to complete clinical remission. In the international Primary Aldosteronism Surgical Outcomes (PASO) cohort, complete biochemical success was achieved in approximately 94% of patients, whereas complete clinical success was observed in approximately 37%.[19] Thus, patients should be counseled that successful elimination of autonomous aldosterone secretion may substantially improve blood pressure and reduce medication burden without necessarily resulting in complete resolution of hypertension.

Post-adrenalectomy renal function changes and their clinical implications

A postoperative increase in serum creatinine is common after adrenalectomy for primary aldosteronism and generally reflects reversal of aldosterone-associated glomerular hyperfiltration, thereby unmasking preexisting renal dysfunction.[14] This anticipated change should be discussed with patients before surgery to avoid unnecessary concern and to provide an appropriate framework for interpreting postoperative renal function.

In patients with PA, chronic aldosterone excess promotes sodium retention, volume expansion, and glomerular hyperfiltration, which may preserve or mask the decline in estimated renal function despite underlying renal injury. Following surgical correction of aldosterone excess, this hyperfiltration state diminishes, resulting in an expected increase in serum creatinine and a corresponding reduction in estimated glomerular filtration rate.[21]

Patients may understandably be concerned by a higher postoperative serum creatinine; therefore, we find it useful to anticipate this change and discuss the expected trajectory of renal function with patients preoperatively. Factors associated with a greater postoperative increase in serum creatinine include a longer duration of hypertension, lower preoperative serum potassium concentration, and a higher aldosterone-to-renin ratio. Recognizing this physiological change is important for appropriate postoperative interpretation of renal function and for avoiding misclassification of the expected decline in hyperfiltration as acute kidney injury.

Medical management

Patients with bilateral etiology of aldosterone excess or patients that are not surgical candidates are treated medically.

MRAs offer good control of blood pressure in patients with PA by blocking the mineralocorticoid receptor. MRA is part of the nuclear receptor family found in various tissues including collecting ducts of kidneys, blood vessels, and myocardium, among others.[22] The goal of therapy is two-fold: treating high blood pressure and decreasing mineralocorticoid mediated effects. Normal blood pressure is believed to be less than 120 mmHg systolic and 80

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mmHg diastolic, however these targets should be individualized to each patient, and MRAs can be used to achieve goal blood pressures.

Suppressed renin should resolve with adequate MRA therapy and appropriate sodium restriction, typically targeting ≤2,200 mg of sodium daily. The clinical benefit of further MRA dose escalation once the desired renin response has been achieved remains uncertain. Conversely, an unexpectedly high renin level should prompt consideration of excessive sodium restriction, particularly if accompanied by volume depletion or hypotension.

The Primary Aldosteronism Medical Treatment Outcomes (PAMO) consensus defines complete biochemical response as correction of hypokalemia (without the need for supplementation) and normalization of renin (PRA > 1 ng/ml/h) or direct renin concentration (DRC) > 8.2-10 mU/L.[23]

First generation steroidal Mineralocorticoid Receptor Antagonist (MRA) spironolactone

Spironolactone is a potassium sparing steroidal MRA that offers potent effects at a low cost.

Spironolactone is a non-selective synthetic steroid and its blocking action cross-reacts with the androgen and progesterone receptor.[7] In males, this can present as symptoms of hypogonadism, although this side effect is dose dependent. Due to its teratogenic effects, spironolactone must be avoided in women planning pregnancy.

Second generation steroidal MRA: Eplerenone

Eplerenone is a steroidal partial MRA with low affinity for androgen and progesterone receptors. It is a suitable alternative for men. Eplerenone is roughly half as potent as spironolactone and requires twice daily dosing.[24]

Novel non-steroidal MRA: finerenone

While primarily studied and approved to reduce adverse cardiovascular and renal outcomes in patients with type 2 diabetes mellitus and chronic kidney disease, its potential application for patients with PA is expanding.[25]

Finerenone is a nonsteroidal MRA with minimal activity on androgen and progesterone receptors. In case of renal disease, the dose should be reduced. Finerenone is approved for the prevention of cardiovascular disease, heart failure exacerbations, and prevention of progressive nephropathy in patients with type 2 diabetes mellitus.[25]

Aldosterone Synthase Inhibitor (ASI): Baxdrostat

ASI represent a novel therapeutic class of drugs that act by directly suppressing the enzymatic production of aldosterone. Unlike traditional MRAs that block aldosterone binding at the receptor level, ASIs selectively inhibit the mitochondrial enzyme CYP11B2 responsible for the final steps of aldosterone synthesis in the adrenal cortex. Baxdrostat was approved by the FDA in 2026 for the treatment of hypertension in combination with other antihypertensive drugs for adults inadequately controlled on other agents, and currently it is the only medication on the market in this drug class. The phase 3 placebo-controlled study, BaxHTN trial, showed about 9-10 mmHg reduction in systolic blood pressure.[26] About 2-3% of patients experienced hyperkalemia above 6 mmol/L.[27] This may be another good choice of medication inpatients with diminished renal function although more data is needed to ascertain safety in patients with kidney disease.

Monitoring therapeutic efficacy when patients are treated with MRAs

The goal of therapy is to mitigate aldosterone excess and mineralocorticoid activity by antagonizing the receptor. One marker of adequate activity is rising renin levels indicating alleviation of aldosterone's suppressive effect on juxtaglomerular cells. Medications can be titrated to bring PRA levels above 1 ng/mL/h or DRC levels above 8.2 mU/L. These goals are achieved by appropriate dose titration of the MRAs and with a sodium restricted diet, typically not exceeding 2,500 mg of sodium daily.[1–7]

Monitoring therapeutic efficacy when patients are treated with ASIs

Baxdrostat (FDA approved in 2026) and lorundrostat lower aldosterone biosynthesis, and the central monitoring priorities during their use are serum potassium, serum sodium (risk of hyponatremia), renal function (eGFR), and blood pressure.[27,28] Aldosterone and renin measurements are clinically useful although the FDA label does not list these as required safety laboratory tests.

In the baxdrostat PA data (SPARK-PA/phase 2a) plasma renin activity rose progressively and the aldosterone-to-renin ratio decreased consistent with complete biochemical response. In patients with resistant hypertension trials, PRA increased versus patients on placebo.[24,29]

Individualize therapy

Treatment for primary aldosteronism should be individualized to each patient. It is our responsibility to explain to our patients in detail to support reasonable shared decision-making steps. Factors that can impact choice of therapy includes age, sex, concomitant mild autonomous cortisol secretion, co-morbidities, surgical candidacy, renal disease, tolerance of oral medications, patient preferences among others. General category of treatment options includes surgery vs medical management. Medical options include spironolactone, finerenone, eplerenone and baxdrostat in addition to other anti-hypertensive agents.[1,7,20]

Histopathology and somatic mutations: defining aldosterone-producing cell subtypes

Histopathology involves the microscopic examination of tissue to identify cellular and structural abnormalities and to characterize the nature of an adrenal lesion. In PA, the HISTALDO (Histopathology of Primary Aldosteronism) consensus classification provides a standardized framework for the histopathologic evaluation of adrenal lesions associated with unilateral PA.[30,31] Importantly, HISTALDO incorporates immunohistochemical staining for CYP11B2 (aldosterone synthase) to identify aldosterone-producing cells and lesions that may not be readily recognized by conventional hematoxylin and eosin staining alone and should be routine practice.[30,31] The classification includes aldosterone-producing adenomas (APAs), aldosterone-producing nodules (APNs), and aldosterone-producing micronodules (APMs), formerly termed aldosterone-producing cell clusters (APCCs), as well as other patterns of aldosterone-producing lesions.

Somatic mutations are acquired genetic alterations that arise in individual cells after conception and are not generally present throughout the germline. In PA, identification of somatic mutations in aldosterone-producing lesions provides important insight into the molecular mechanisms underlying autonomous aldosterone production and contributes to our understanding of genotype–

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phenotype relationships. Somatic mutations have been identified not only in APAs but also in aldosterone-producing nodules and micronodules, supporting the concept that aldosterone-producing lesions represent a biologically heterogeneous spectrum.[32,33]

Somatic mutations identified in APAs include KCNJ5, encoding an inwardly rectifying potassium channel; CACNA1D, encoding a voltage-gated calcium channel; ATP1A1, encoding the α1 subunit of the Na^+/K^+-ATPase; ATP2B3, encoding a plasma membrane calcium ATPase; and CTNNB1, encoding β-catenin.[32,33] These mutations affect ion transport, membrane potential, intracellular calcium signaling, or downstream pathways that promote CYP11B2 expression and autonomous aldosterone synthesis**.**

Somatic aldosterone-driver mutations have also been identified in APMs/APCCs and in selected aldosterone-producing nodules and areas of hyperplasia. Of particular interest, CACNA1D mutations are frequently identified in aldosterone-producing micronodules, including lesions found in individuals without overt PA, suggesting that genetically altered aldosterone-producing cell populations may occur along a continuum from apparently normal adrenal cortex to micronodules and clinically manifest aldosterone excess.[33]

More than 90% of aldosterone-producing adenomas (APAs) harbor somatic driver mutations in genes encoding ion channels, pumps, or signaling proteins.[34,33] The most frequently mutated genes include KCNJ5 (found in 10–68% of APAs, more common in younger female patients and in Asian populations), CACNA1D, ATP1A1, ATP2B3, and CTNNB1, with rarer mutations in CACNA1H, CLCN2, GNAQ/11, and SLC30A1.[35] There is increasing interest in targeting these mutations therapeutically. For KCNJ5-mutated adenomas, macrolide antibiotics (including roxithromycin and clarithromycin) have been shown to selectively inhibit mutant KCNJ5 channels, reducing CYP11B2 expression and aldosterone secretion in vitro and ex vivo without affecting wild-type channels.[34] This has raised the possibility of precision medical therapy for KCNJ5-mutated APAs, a hypothesis currently being tested in clinical studies such as the macrolides for *KCNJ5* – mutated aldosterone producing adenomas (MAPA) trial.[36]

As of now, somatic mutation analysis and mutation-directed therapeutics remain confined to the research setting and are not yet part of routine clinical pathology evaluation.

Thus, integrating histopathology, *CYP11B2* immunohistochemistry, and molecular characterization is advancing our understanding of the cellular and molecular heterogeneity of PA. The HISTALDO framework[30] has an important role in standardizing pathology terminology and improving consistency in the identification and classification of aldosterone-producing lesions. Emerging evidence also suggests that histopathologic patterns may be associated with postoperative biochemical and clinical outcomes; however, the prognostic value of specific somatic mutations remains an evolving area of investigation.

Germline genetics, precision medicine and familial forms of primary aldosteronism: every patient with primary aldosteronism deserves a family history

Recognizing familial forms of PA begins with the family history requiring a thorough family history in every patient. Clinicians should specifically ask about first and second-degree relatives with early-onset or resistant hypertension, hypokalemia, PA, adrenal tumors, or cerebrovascular events, particularly hemorrhagic stroke at a young age, which is a recognized complication of familial hyperaldosteronism (FH) Type I.[30]

Patients with FH-I, a autosomal dominant chimeric gene FH-I, or glucocorticoid-remediable aldosteronism (GRA), results from an unequal crossover between *CYP11B1* and *CYP11B2*, generating a chimeric gene in which aldosterone synthase activity becomes regulated by ACTH.[30] Consequently, aldosterone production can be suppressed with glucocorticoid therapy although in practice we treat GRA with MRAs to avoid lifelong exposure to glucocorticoids.

FH-II is caused by autosomal dominant germline pathogenic variants in *CLCN2*, which encodes the voltage-gated chloride channel. Increased chloride efflux from zona glomerulosa cells promotes membrane depolarization, activation of voltage-gated calcium channels, and increased intracellular calcium, thereby stimulating *CYP11B2* expression and aldosterone production.[30]

FH-III also has autosomal dominant inheritance resulting from germline pathogenic variants in *KCNJ5*, encoding the inwardly rectifying potassium channel GIRK4. These variants alter channel ion selectivity, permitting increased sodium influx, membrane depolarization, and subsequent calcium influx.[30]

FH-IV is a germline pathogenic variants in *CACNA1H*, which encodes the T-type calcium channel CaV3.2 which is a gain-of-function variant causing an increase in calcium influx and stimulates aldosterone production.[30]

A related but distinct genetic syndrome, primary aldosteronism, seizures, and neurological abnormalities (PASNA), is associated with germline, often de novo, pathogenic variants in *CACNA1D*, which encodes the L-type calcium channel CaV1.3. These gain-of-function variants directly increase calcium influx and may produce PA accompanied by seizures and other neurological manifestations.[30]

The identification of these molecular subtypes has transformed our understanding of familial PA. What was historically considered a relatively heterogeneous group of familial or early-onset PA has progressively been dissected into genetically defined entities through molecular and next-generation sequencing approaches. Importantly, these disorders differ in age of presentation, severity of PA, associated clinical manifestations, and therapeutic considerations. Recognition of familial forms therefore has implications not only for individualized treatment but also for genetic counseling and screening of at-risk family members.[30] The 2025 Endocrine Society Clinical Practice Guideline recommends genetic testing in individuals with PA diagnosed before age 20 years and genetic screening of first-degree relatives of individuals with a confirmed familial form of PA.[7,30,37]

Conclusion

The clinical consequences of PA extends well beyond blood pressure elevation therefore it is important to screen all patients with hypertension regardless of severity of their hypertension or potassium levels. Successful treatment should therefore aim not only to control blood pressure but also to eliminate or antagonize the pathologic effects of aldosterone excess and mitigate its associated target-organ injury.

Recognizing this phenotypic heterogeneity is essential for individualized diagnostic evaluation, interpretation of biochemical testing, selection of appropriate therapy, and long-term follow-up to optimize blood pressure control, biochemical outcomes, cardiovascular and renal health, and overall patient well-being.

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Our responsibility therefore extends beyond diagnosing PA. We must also help patients understand what the diagnosis means, why treatment matters, and how available therapeutic options can best align with their best individual goals and assist in shared decision making. In patients with hypertension, identifying a specific and potentially treatable subtype can transform patient care.

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Conflicts of interest

No conflict of interests to disclose.

References

1. Lassen MCH, Ostrominski JW, Claggett BL, et al. Spectrum of primary aldosteronism and risk of cardiovascular outcomes: the Atherosclerosis Risk in Communities Study. *JAMA Cardiol.* 2026;11(4):341–351.
2. Selye H, Hall CE, Rowley EM. Production of nephrosclerosis by overdosage with deoxycorticosterone acetate. *Can Med Assoc J.* 1942;47(6):515–519.
3. Grundy H, Simpson S, Tait J. Isolation of a highly active mineralocorticoid from beef adrenal extract. *Nature.* 1952;169(4306):795–796.
4. Simpson SA, Tait JF, Wettstein A, et al. Constitution of aldosterone, a new mineralocorticoid. *Experientia.* 1954;10(3):132–133.
5. Conn JW. Presidential address II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med.* 1955;45(1):3–17.
6. Ladd MR, Zeiger MA. Who was Dr. William C. Baum? *World J Surg.* 2018;42(8):2437-2443.
7. Adler GK, Stowasser M, Correa RR, et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2025;110(9):2453–2495.
8. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med.* 2001;345(23):1689–1697.
9. Brown JM, Auchus RJ, Honzel B, et al. Recalibrating interpretations of aldosterone assays across the physiologic range: immunoassay and liquid chromatography-tandem mass spectrometry measurements under multiple controlled conditions. *J Endocr Soc.* 2022;6(6).
10. Baudrand R, Vaidya A. The low-renin hypertension phenotype: genetics and the role of the mineralocorticoid receptor. *Int J Mol Sci.* 2018;19(2):546.
11. Vasbinder M, Kuindersma M, Mulder AH, et al. The influence of oral contraceptives on overnight 1 mg dexamethasone suppression test. *Neth J Med.* 2016;74(4):158–161.
12. Alvarez-Payares JC, Bello-Simanca JD, De La Peña-Arrieta EDJ, et al. Common pitfalls in the interpretation of endocrine tests. *Front Endocrinol (Lausanne).* 2021;12:727628.
13. Doppman JL, Gill JR Jr. Hyperaldosteronism: sampling the adrenal veins. *Radiology.* 1996;198(2):309–312.
14. Shteyman S, Aftab H, Tendler B. Adrenal venous sampling: practical insights and case studies. *Urol Clin North Am.* 2025;52(2):253–260.
15. Nanba AT, Warnachalee T, Shields JJ, et al. Adrenal vein sampling lateralization despite mineralocorticoid receptor antagonist exposure in primary aldosteronism. *J Clin Endocrinol Metab.* 2019;104(2):309–312.
16. Wu VC, Wang SM, Huang KH, et al. Long-term mortality and cardiovascular events in patients with unilateral primary aldosteronism after targeted treatments. *Eur J Endocrinol.* 2021;186(2):195–205.
17. Samnani S, Cenzer I, Kline GA, et al. Time to benefit of surgery vs targeted medical therapy for patients with primary aldosteronism: a meta-analysis. *J Clin Endocrinol Metab.* 2024;109(3):e1280–e1289.
18. Williams TA, Lenders JWM, Mulatero P, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol.* 2017;5(9):689–699.
19. Miller B, Turcu A, Nanba T, et al. Refining the definitions of biochemical and clinical cure for primary aldosteronism using the Primary Aldosteronism Surgical Outcome (PASO) classification system. *World J Surg.* 2018;42(2):453-463.
20. Hundemer GL, Vaidya A. Primary aldosteronism diagnosis and management: a clinical approach. *Endocrinol Metab Clin North Am.* 2019;48(4):681–700.
21. Tomiie Y, Hibi Y, Nobe R, et al. Changes in kidney function after adrenalectomy in patients with primary aldosteronism. *Fujita Med J.* 2024;11(1):28–35.
22. Koca D, Lother A. Molecular pharmacology of mineralocorticoid receptor antagonists: the role of co-regulators. *Steroids.* 2023;199:109291.
23. Yang J, Burrello J, Goi J, et al; PAMO Investigators. Primary aldosteronism medical outcomes: an international consensus. *J Endocr Soc.* 2024;8(suppl 1).604.
24. Parthasarathy HK, Ménard J, White WB, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens.* 2011;29(5):980–990.
25. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(23):2219–2229.
26. Bloch MJ, Basile JN. Spironolactone is more effective than eplerenone at lowering blood pressure in patients with primary aldosteronism. *J Clin Hypertens (Greenwich).* 2011;13(8):629–631.
27. Flack JM, Azizi M, Brown JM, et al. Efficacy and safety of baxdrostat in uncontrolled and resistant hypertension. *N Engl J Med.* 2025;393(14):1363–1374.
28. Laffin LJ, Kopjar B, Melgaard C, et al; Advance-HTN Investigators. Lorundrostat efficacy and safety in patients with uncontrolled hypertension. *N Engl J Med.* 2025;392(18):1813–1823.
29. Turcu AF, Freeman MW, Bancos I, et al. Phase 2a study of baxdrostat in primary aldosteronism. *N Engl J Med.* 2025;393(3):515–518.
30. Vedere T, Khalifa M. A comprehensive review of pathophysiology, diagnosis, and treatment. *Urol Clin North Am.* 2025;52(2):205–216.
31. Williams TA, Gomez-Sanchez CE, Rainey WE, et al. International histopathology consensus for unilateral primary aldosteronism. *J Clin Endocrinol Metab.* 2021;106(1):42–54.
32. Lim JS, Wu CY, Qin Z, et al. Increased frequency and distinct genotypic patterns of somatic aldosterone-driver mutations in aldosterone-producing micronodules from primary aldosteronism patients. *Endocr Pathol.* 2026;37(1):16.
33. Scholl UI. Genetics of primary aldosteronism. *Hypertension.* 2022;79(5):887–897.
34. Scholl UI, Abriola L, Zhang C, et al. Macrolides selectively inhibit mutant KCNJ5 potassium channels that cause aldosterone-producing adenoma. *J Clin Invest.* 2017;127(7):2739–2750

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35. Fernandes-Rosa FL, Williams TA, Riester A, et al. Genetic spectrum and clinical correlates of somatic mutations in aldosterone-producing adenoma. *Hypertension.* 2014;64(2):354–361.

36. US National Library of Medicine. Clinical trial registry record for NCT03414918. ClinicalTrials.gov. Updated August 25, 2026. Accessed August 25, 2026.

37. Taylor GA, Allen M, Lisevick Kumar A, et al. Adrenalectomy patients with mixed primary aldosteronism and hypercortisolism: an analysis of outcomes following surgery at a single institution. *Surgery.* 2026;189:109855.

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