2023 Korean Endocrine Society Consensus Guidelines for the Diagnosis and Management of Primary Aldosteronism

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Primary aldosteronism (PA) is a common, yet underdiagnosed cause of secondary hypertension. It is characterized by an overproduction of aldosterone, leading to hypertension and/or hypokalemia. Despite affecting between 5.9% and 34% of patients with hypertension, PA is frequently missed due to a lack of clinical awareness and systematic screening, which can result in significant cardiovascular complications. To address this, medical societies have developed clinical practice guidelines to improve the management of hypertension and PA. The Korean Endocrine Society, drawing on a wealth of research, has formulated new guidelines for PA. A task force has been established to prepare PA guidelines, which encompass epidemiology, pathophysiology, clinical presentation, diagnosis, treatment, and follow-up care. The Korean clinical guidelines for PA aim to deliver an evidence-based protocol for PA diagnosis, treatment, and patient monitoring. These guidelines are anticipated to ease the burden of this potentially curable condition.

INTRODUCTION

Primary aldosteronism (PA) is a common and treatable form of secondary hypertension. It is characterized by excessive, autonomous aldosterone secretion from adrenal glands. This leads to the retention of sodium and the excretion of potassium, resulting in hypertension and hypokalemia. It has been estimated that 5.9% to 34% of all patients with hypertension may actually have PA, underscoring the importance of precise diagnosis and management [1]. Despite the high prevalence, PA remains underdiagnosed and undertreated, leading to significant cardiovascular morbidity and mortality. This can be attributed to a lack of clinical awareness and systematic screening protocols, which can lead to delayed or missed diagnoses. Given the importance of PA in managing hypertension, various medical societies have published clinical practice guidelines, leading to significant improvements in the clinical practice of hypertension and PA. Large-scale multi-center clinical studies have provided substantial evidence that supports the need for the development of new clinical practice guidelines by the Korean Endocrine Society. As a result, we have appointed a task force to prepare updated guidelines for PA in Korea. The consensus statement is divided into sections that cover the epidemiology, pathophysiology, clinical presentation, diagnostic work-up, treatment, and follow-up care of patients with PA. Each section will present the most recent scientific evidence and expert consensus.

The Korean clinical guidelines for PA aim to provide an evidence-based approach to the diagnosis, treatment, and follow-up of patients with PA. The guidelines will aid healthcare professionals in identifying PA, selecting the most suitable diagnostic tests, determining the most effective treatment plans, and delivering superior follow-up care. This consensus statement aims to alleviate the impact of this potentially treatable form of hypertension and enhance patient care quality, ultimately resulting in improved patient outcomes.

DEFINITION OF PRIMARY ALDOSTERONISM

PA is the most common endocrine cause of secondary hypertension. It characterized by the autonomous production of aldosterone, which is a mineralocorticoid hormone that serves as a crucial end-effector of the renin-angiotensin system (RAS). Aldosterone is responsible for the regulation of extracellular volume, blood pressure (BP), and potassium levels. Angiotensin II, which binds to angiotensin type 1 receptor (AT1R), is a potent stimulus

for aldosterone secretion from the zona glomerulosa of the adrenal glands. Aldosterone secretion is also triggered by elevated serum potassium and, to a lesser extent, by adrenocorticotropic hormone (ACTH) [2]. Aldosterone diffuses through the cell membrane and then binds to the mineralocorticoid receptor (MR), stimulating the expression and activity of several channels/transporters. The electrochemical gradient resulting from reabsorption of sodium causes secretion of potassium into the urine via apical potassium channels [3]. PA was first described by Conn [4] in 1954. It refers to a pathophysiological condition that is characterized by the autonomous production of aldosterone independent of the renin-angiotensin II. This condition can lead to increased sodium reabsorption in the renal tubule and volume expansion, resulting in hypertension and/or hypokalemia. High delivery of sodium chloride to the juxtaglomerular apparatus and elevated systemic BP can suppress renin secretion, leading to an increase in the aldosterone-to-renin ratio (ARR). Therefore, PA is the most frequent cause of secondary hypertension [5]. In PA, aldosterone secretion remains persistently high despite adequate blood volume and BP, reflecting its autonomous and inappropriate production. Variations in BP and potassium levels are noteworthy aspects of PA, influenced by multiple factors such as glomerular filtration, distal tubular sodium delivery, arterial compliance, and the duration and magnitude of aldosterone excess. The severity and duration of PA are usually associated with the likelihood of severe hypertension and/or hypokalemia. PA is a predisposing factor for cardiovascular disease, cerebrovascular, renal, metabolic, and bone mineral-related sequelae, including myocardial infarction, heart failure, atrial fibrillation (AF), stroke, sarcopenia and chronic kidney disease [1,6-12]. PA is mainly categorized into two clinical subtypes: (1) unilateral hyperaldosteronism, including unilateral aldosterone-producing adenoma (APA) or unilateral adrenal hyperplasia (UAH); and (2) bilateral hyperaldosteronism, including idiopathic bilateral adrenal hyperplasia (IAH) and bilateral APA.

PREVALENCE OF PRIMARY ALDOSTERONISM

The estimated prevalence rate of PA among individuals with hypertension ranges from 5.9% to 34% [1,13]. Once considered a rare disease, affecting less than 1% of the population [14], PA is now recognized as more prevalent than previously thought. Comprehensive screening studies conducted in diverse primary care settings across various countries have found prevalence rates for PA ranging from 0.7% to 14% [15-17]. In contrast, the

prevalence at referral or tertiary centers has been reported to be as high as 29.8% [18]. Thus, PA prevalence estimates vary significantly. The incidence of PA has been found to increase with age [19]. This variation can be attributed to differences in the diagnostic criteria used to define the condition. Specifically, stricter diagnostic thresholds are associated with a lower reported prevalence. For instance, a potential prevalence of 13.8% has been estimated using a diagnostic threshold of an aldosterone level above 10 ng/dL and an ARR above 30 ng/dL per ng/mL/ hr. However, when the diagnostic threshold was relaxed to an ARR >20 ng/dL per ng/mL/hr and the requirement for a minimum aldosterone concentration was removed, the prevalence increased to 33% [1]. The prevalence of PA potentially increases with the severity of hypertension. Systematic reviews have reported a range of prevalence rates for PA among individuals with hypertension, from 3.2% to 12.7% in primary care settings, and from 1% to 29.8% in referral centers [18]. Based on confirmatory testing, the adjusted prevalence has been found to be 11.3% in normotensive individuals, but 22.0% in patients with refractory hypertension [20]. A recent Korean tertiary care-based study reported a prevalence rate of 6.1% for confirmed PA [21]. When analyzed based on the severity of hypertension, the weighted mean prevalence of PA was found to be 5.5% in patients with high-normal BP, 4.2% in those with stage 1 hypertension, 10.2% in those with stage 2 hypertension, and 16.4% in those with stage 3 hypertension [22]. However, it is important to note that certain antihypertensive agents, such as mineralocorticoid receptor antagonists (MRAs), might mask the presence of PA. Moreover, hypokalemia was observed in less than 40% (range, 9% to 37%) of PA patients [15]. Therefore, relying exclusively on hypokalemia as the primary indicator for diagnostic testing might lead to the underdiagnosis of PA. Nevertheless, the presence of hypokalemia mandates screening for PA. The reported prevalence of PA in patients with adrenal incidentaloma ranges from 1.0% to 4.0% [23]. PA is also associated with obesity, obstructive sleep apnea (OSA), and diabetes mellitus. A recent cross-sectional multi-ethnic study enrolled 203 individuals diagnosed with OSA and found that the prevalence of PA was 8.9% [24]. Thus, PA might manifest as a spectrum of clinical presentations, with milder phenotypes potentially observed in normotensive individuals. Therefore, the selection of a screening test cut-off that optimizes sensitivity and specificity, while allowing for subsequent confirmation of positive cases and exclusion of false positives, is of the utmost importance.

CASE DETECTION: WHO SHOULD BE SCREENED FOR PRIMARY ALDOSTERONISM?

It is strongly advised to screen all patients with hypertension due to the high prevalence of PA and the significant correlations of PA with unfavorable cardiovascular and renal outcomes. The consensus opinion among international guidelines, including the Endocrine Society [25], the American College of Cardiology/ American Heart Association [26], the European Society of Hypertension [27], and the Japan Endocrine Society [28], strongly supports screening for PA in patient groups with a high prevalence of this condition. Factors associated with a high prevalence of PA include treatment-resistant hypertension, hypertension with hypokalemia, adrenal incidentaloma or sleep apnea, family history of early-onset hypertension or cerebrovascular events at young age (<40 years), and a family history of PA. However, the definition of an optimal BP threshold for diagnosing hypertension and the recommended BP targets for individuals with hypertension have been continually revised and updated over the past decade. The median age at diagnosis in most prevalence studies ranged from 50 to 55 years. In a study conducted in India, 17.8% of hypertensive patients who had an onset of hypertension before the age of 40 were confirmed to have PA [29].

Indications for PA screening with any criteria

(1) Sustained BP above 160/100 mm Hg, measured on three consecutive measurements on different days
(2) Hypertension resistant (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) to three conventional antihypertensive drugs
(3) Controlled BP on four or more antihypertensive drugs
(4) Hypertension at a younger age (<40 years)
(5) Hypertension and hypokalemia (spontaneous or diuretic-induced)
(6) Hypertension and an adrenal tumor
(7) Hypertension and lone AF
(8) Hypertension and a family history of early-onset hypertension or cerebrovascular event at a young age (<40 years)
(9) Hypertension in first-degree relatives of patients with PA

GENETICS

Next-generation sequencing research has recently revealed that PA is predominantly a genetic disorder [30]. Somatic mutations,

primarily in ion channels and pumps, are responsible for sporadic cases, while familial hyperaldosteronism (FH) arises from germline mutations in a similar group of genes.

Somatic mutations in sporadic primary aldosteronism
The majority (more than 90%) of APAs exhibit somatic mutations in genes such as potassium channel Kir3.4 (*KCNJ5*) [31], calcium channel CaV1.3 (*CACNA1D*) [32], alpha-1 subunit of the sodium-potassium ATPase (*ATP1A1*), plasma membrane calcium-transporting ATPase 3 (*ATP2B3*) [33], calcium channel CaV3.2 (*CACNA1H*) [34], chloride channel ClC-2 (*CLCN2*), β-catenin (*CTNNB1*) [35,36], and G-protein subunits alpha q/11 (*GNAQ/11*) [37]. Most of these mutations result in adrenal cell depolarization or a direct increase in intracellular Ca^{2+} concentration, leading to continuous aldosterone production or cell proliferation in the case of *CTNNB1* gene mutations. The mutational profile of APAs depends on their cells of origin, which might differ according to sex and ethnicity [38]. The prevalence of *KCNJ5* mutations has been reported to be 71.2% in Korean patients, similar to those in other Asians [39]. Some of these gene mutations have also been discovered in aldosterone-producing (micro) nodules, suggesting that disease progresses from a single cell to a nodule with adenoma formation and from a healthy state to subclinical and overt forms. Each adrenal gland may contain multiple such lesions. Bilateral disease can involve both glands.

Germline mutations in familial primary aldosteronism
Approximately 5% of patients with PA may exhibit FH [40]. Genetic testing for FH is recommended for patients with early-onset and a family history of PA [30]. Germline mutations in genes such as steroid 11-beta hydroxylase/aldosterone synthase (*CYP11B1/2*), *CLCN2, KCNJ5, CACNA1H*, and *CACNA1D* can lead to genetic forms of PA. Familial hyperaldosteronism type I (FH-I or glucocorticoid-remediable aldosteronism) is the most prevalent form of monogenic hypertension [41,42]. It is diagnosed by using long-range polymerase chain reaction to amplify the chimeric *CYP11B1/CYP11B2*. The treatment of choice is a low dose of dexamethasone (such as 0.125 to 0.25 mg) to suppress ACTH or in combination with MRAs [25]. FH-II is caused by germline mutations in the *CLCN2* gene encoding voltage-gated chloride channel 2. It exhibits incomplete penetrance [43, 44]. Mutant chloride channels can lead to Cl- efflux, cell depolarization, and CYP11B2 overexpression. Its diagnosis relies on sequencing of the *CLCN2* gene. FH-III is caused by germline mutations in the *KCNJ5* gene [31]. These mutations result in the loss of K^+ selectivity, Na^+ entry, cell membrane depolarization, and the opening of voltage-gated Ca^{2+} channels, leading to increased intracellular Ca^{2+} levels, upregulation of CYP11B2 expression, and aldosterone overproduction [31]. FH-III should be excluded in all patients with very early-onset PA [25]. Genetic testing is conducted by direct *KCNJ5* sequencing. FH-IV is a rare condition caused by germline mutations in the *CACNA1H* gene [34], which encodes the pore-forming α subunit of the T-type calcium channel, Cav3.2. This gain-of-function mutation shows incomplete penetrance. It can increase calcium influx and induce autonomous aldosterone overproduction. It is diagnosed by targeted sequencing of the *CACNA1H* gene. Primary aldosteronism with seizures and neurologic abnormalities (PASNA) syndrome is a genetic but non-familial type of PA caused by a *de novo* gain-of-function mutation in the *CACNA1D* gene, which encodes the α1D subunit of the L-type voltage-gated calcium channel Cav1.3 [32]. Due to the severity of neurological manifestations, patients are unlikely to reproduce. Its diagnosis is made by targeted sequencing of the *CACNA1D* gene. The subtypes of familial hyperaldosteronism are summarized in Table 1. We propose that genetic testing can be conducted for all patients with early-onset PA (i.e., onset before 20 years of age) regardless of the clinical phenotype's severity and for patients who have a documented familial history of PA.

Table 1. Familial Hyperaldosteronism Subtypes

Subtypes	Disease genes	Specific features	Therapy
FH-I	*CYP11B1/CYP11B2*	Responds to dexamethasone, hybrid steroids	Dexamethasone, MRA
FH-II	*CLCN2*	None	MRA
FH-III	*KCNJ5*	Variable hyperplasia, hybrid steroids	MRA, bilateral adrenalectomy
FH-IV	*CACNA1H*	None	MRA
PASNA	*CACNA1D*	Seizures, neurological abnormalities, heart defects, transient hypoglycemia (variable)	MRA, calcium antagonists (?)

FH, familial hyperaldosteronism; MRA, mineralocorticoid receptor antagonist; PASNA, primary aldosteronism with seizures and neurologic abnormalities.

DIAGNOSIS OF PRIMARY ALDOSTERONISM

Plasma renin and aldosterone assays

Plasma renin can be assessed as either plasma renin activity (PRA, ng/mL/hr) by measuring the catalytic activity or renin to produce angiotensin I or direct renin concentration (DRC, mIU/L or pg/mL). DRC is measured using an immunoradiometric assay or automated chemiluminescence immunometric assay, which measures the number of active renin molecules independent of enzymatic activity. DRC measurement is a cost- and time-effective method, showing superior between-laboratory reproducibility. It is known as a reliable alternative to PRA [45,46]. Unfortunately, DRC is not yet commercially available in Korea, so it cannot be used in clinical practice. Although PRA is a complex and labor-intensive method, it is accurate for determining very low renin levels (PRA <1 ng/mL/hr), which occur in patients with PA [47]. However, since all available methods are inaccurate in states of very low renin levels, it is a common practice to set the low detection limit at 0.2 ng/mL/hr for PRA or 2 mIU/L for DRC [48]. The plasma aldosterone concentration (PAC, ng/dL or pmol/L) can be measured by radioimmunoassay, automated chemiluminescent assay, or liquid chromatography and tandem mass spectrometry (LC-MS/MS) [49,50]. Although LC-MS/MS can substantially increase the analytical accuracy of PAC measurements, it is not yet widely available [51]. Automated chemiluminescent assays enable rapid and accurate simultaneous measurements of both DRC and PAC using only 200 µL of plasma with a high within-assay reproducibility [46].

Screening test: plasma aldosterone-to-renin ratio

The accepted screening test for PA is the calculation of the plasma ARR. The ARR has better sensitivity and specificity than the measurement of plasma aldosterone, renin, and potassium concentrations alone [52-54]. ARR thresholds differ depending on the assay method and unit of measure for renin and PAC (Table 2). The most commonly adopted cut-off to define a positive ARR is 30, when aldosterone is measured in ng/dL and PRA is measured in ng/mL/hr. However, the ARR might yield a false-positive result in the presence of very low renin levels even when the PAC is also low. To avoid this false positivity, some investigators have included a minimum PAC of >15 ng/dL within the screening criteria [55-57]. However, several studies have reported that the PAC was <15 ng/dL in 30% to 40% of patients with PA who

Table 2. ARR Cut-off Values Depending on Assay and Unit of Measure for Renin and PAC

	PRA, ng/mL/hr	DRC, mIU/L[a]
PAC, ng/dL	20	2.4
	30	3.7
	40	4.9
PAC, pmol/L[b]	550	67
	830	101
	1,100	134

ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity; DRC, direct renin concentration.
[a]Values shown are on the basis of a conversion factor that is generally used to convert PRA (ng/mL/hr) to DRC (mU/L) is 8.2. However, the conversion factor is 12 when the recently introduced and already widely used Diasorin immunoassay is used; [b]The adopted conversion factor of 1 ng/dL of aldosterone is 27.7 pmol/L.

Table 3. Drugs and Other Factors that Influence the ARR

Factors	Effect on aldosterone	Effect on renin	Net effect on ARR
Drugs			
ACE inhibitors, ARBs	↓	↑↑	↓ (FN)
Central α_2-agonist (clonidine, α-methyldopa)	↓	↓↓	↑ (FP)
K^+ sparing diuretics (MRAs, amiloride)	↑	↑↑	↓ (FN)
K^+ wasting diuretics (thiazides, loop diuretics)	→ or ↑	↑↑	↓ (FN)
β-Blockers	↓	↓↓	↑ (FP)
CCBs (DHPs)	→ or ↓	↑	↓ (FN)
NSAIDs	↓	↓↓	↑ (FP)
Sodium and potassium status			
Sodium restriction	↑	↑↑	↓ (FN)
High-sodium diet	↓	↓↓	↑ (FP)
Hypokalemia	↓	→ or ↑	↓ (FN)
Potassium loading	↑	→ or ↓	↑ (FP)
Other clinical conditions			
Old age	↓	↓↓	↑ (FP)
Pregnancy	↑	↑↑	↓ (FN)
Renal impairment	→	↓	↑ (FP)
Renovascular HTN, malignant HTN	↑	↑↑	↓ (FN)

Adapted from Funder et al. [25].
ARR, aldosterone-to-renin ratio; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; ↑, increased; ↓, decreased; FN, false-negative; FP, false-positive; MRA, mineralocorticoid receptor antagonist; →, unchanged; CCB, calcium channel blocker; DHP, dihydropyridine; NSAID, non-steroidal anti-inflammatory drug; HTN, hypertension.

tested positive with the ARR [58,59].

Factors that influence the aldosterone-to renin ratio
Table 3 presents a list of medications and other clinical conditions that can affect the ARR. Several antihypertensive drugs can alter the regulation of the RAS and plasma renin and aldosterone levels [60]. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can stimulate renin and decrease PAC, thereby lowering the ARR, while β-blockers can suppress renin, resulting in a false-positive ARR [60]. Diuretics can cause volume depletion, which can elevate renin and, to a lesser degree, aldosterone, resulting in a false-negative ARR. It is well known that under physiological conditions, a high-sodium diet can reduce renin secretion more than aldosterone secretion, potentially leading to false-positive results. Conversely, a low-sodium diet can increase plasma renin and, to a lesser extent, aldosterone levels, leading to false-negative ARR results. Changes in extracellular potassium concentrations also have a major impact on the control of aldosterone secretion, with hypokalemia lowering the PAC. In patients aged >65 years, renin can be lowered more than aldosterone by age alone, leading to false-positive ARR results [25]. Therefore, these factors should be considered when interpreting the ARR. If the initial ARR is inconclusive due to these confounding factors, the ARR test should be repeated.

Preparation of patients for ARR measurement
Both renin and aldosterone follow a circadian pattern, with aldosterone levels being the highest upon awakening in the morning [61]. Posture can also influence both renin and aldosterone, with an upright position increasing plasma renin levels and thereby increasing the PAC. Therefore, it is usually recommended to collect blood samples in the morning after patients have been seated for 5 to 15 minutes (ideally for at least 15 minutes) [25]. Marked hypokalemia can decrease aldosterone secretion. Therefore, potassium deficiency should be corrected with high oral doses of potassium chloride before measuring the ARR. Additionally, patients should have unrestricted dietary salt intake before testing. Ideally, it would be preferable to stop interfering drugs before measuring the ARR. In particular, MRAs and β-blockers might be associated with false-negative and false-positive results, respectively, making the ARR difficult to interpret. If a potentially problematic antihypertensive drug cannot be safely withdrawn, the patient should be treated with medications that have only a minimal impact on the ARR (Table 4) [25]. However, research has found that in typical PA, antihypertensive medication does not significantly affect the screening results, and medications including MRAs can be used in patients undergoing screening for PA [62,63]. In many cases, the ARR can be confidently interpreted considering the known effects of antihypertensive medication. The finding of a high PAC and low renin level in patients taking medications expected to increase renin levels and lower the PAC can enable the diagnosis of PA. For instance, PA can be strongly suspected in patients on an MRA if renin is suppressed [64,65], and a medication washout is not needed. If renin is not suppressed, and the pretest probability for PA is high, the withdrawal of the MRA (for a minimum of 4 weeks) and a switch to non-interfering medication should be considered.

Confirmatory tests
Considering the low specificity of the ARR for PA diagnosis, one or more confirmatory tests should be performed. These tests should demonstrate that aldosterone production is not suppressed in response to acute exposure to volume expansion or to blunting angiotensin II synthesis [48]. It has been shown that the specific-

Table 4. Medications with Minimal Effects on Renin and Plasma Aldosterone Concentration

Drug	Class	Usual dose	Comments
Verapamil slow-release	Non-DHP CCB	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table
Hydralazine	Vasodilator	10–12.5 mg twice daily	Commence verapamil slow-release first to prevent reflex tachycardia Commence at low dose to reduce risk of side effect (headaches, flushing, and palpitations)
Prazosin	α-Blocker	0.5–1 mg two or three times daily	Monitor for postural hypotension
Doxazocin	α-Blocker	1–2 mg once daily	Monitor for postural hypotension
Terazosin	α-Blocker	1–2 mg once daily	Monitor for postural hypotension

Adapted from Funder et al. [25].
DHP, dihydropyridine; CCB, calcium channel blocker.

ity of the ARR for PA diagnosis increases and the false-positive rate decreases as ARR values rise [66]. Therefore, confirmatory tests are not necessary for patients with spontaneous hypokalemia, a PAC greater than 20 ng/dL, and plasma renin below detection limits [10,25]. Four testing procedures are currently recommended by the Endocrine Society guidelines (Table 5) [67]. There is not enough evidence to recommend one test over the other. Confirmatory testing, as a screening measure, requires standardized conditions. Hypokalemia should be corrected, and any antihypertensive drugs that may interfere with the test should be replaced with medications that have minimal impact on aldosterone and renin levels (Table 6).

Table 5. Confirmatory Tests for PA

Test and methods	Interpretation	Remarks
Oral sodium loading test (SLT): Sodium intake >200 mmol (6 g)/day for 3 consecutive days	24-hour urinary aldosterone from the morning of day 3 to the morning of day 4: >12 or 14 μg/day: PA highly likely <10 μg/day: PA unlikely	Contraindication: severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, heart failure, or severe hypokalemia Inconvenient 24-hour urine collection and aldosterone measurement by HPLC-MS advisable
Fludrocortisone suppression test (FST): Oral fludrocortisone 0.1 mg every 6 hours for 4 days, together with slow-release KCL supplements, slow-release NaCl supplements (30 mmol three times daily with meal) and sufficient dietary salt	On day 4, Upright PAC >6 ng/dL and PRA <1 ng/mL/hr at 10:00 AM: PA highly likely	Plasma cortisol concentration at 10:00 AM should be lower than the value obtained at 7:00 AM to exclude a confounding ACTH effect.
Saline infusion test (SIT): 4 hours infusion of 2 L of 0.9% NaCl Recumbent position 1 hour before and during test starting at 8:00–9:30 AM or seated position 30 minutes before and during test	Post-infusion PAC: For the recumbent position, >10 ng/dL: PA highly likely 5–10 ng/dL: PA intermediate likely <5 ng/dL: PA unlikely For the seated position, >6 ng/dL: PA confirmed, provided plasma cortisol level is lower than basal cortisol Cut-off value can change depending on the specific assay being used	Contraindication: severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, heart failure, or severe hypokalemia
Captopril challenge test (CCT): 25–50 mg of captopril orally after sitting or standing for 1–2 hours; patient remains seated until test completion	2 hours after captopril: PAC >11 ng/dL and PRA suppressed or ARR >20 ng/dL/ng/mL/hr: PA highly likely PAC <8.5 ng/dL: PA highly unlikely	Substantial number of false-negative or equivocal results

Adapted from Funder et al. [25]; and adapted from Turcu et al. [67], with permission from Springer Nature.
PA, primary aldosteronism; HPLC-MS, high performance liquid chromatography-mass spectrometry; KCL, potassium chloride; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ACTH, adrenocorticotropic hormone; ARR, aldosterone-to-renin ratio.

Table 6. Testing Conditions for ARR Measurements

1. Correct hypokalemia

2. Encourage the patient to liberalize sodium intake

3. Check medication
   1) Current antihypertensive medication can be maintained during screening and the results can be interpreted considering known drug effects.
   2) If the results of the ARR on current medication are not diagnostic or renin suppression is not evident, consider stopping the MRA for 4–6 weeks.
   3) If needed, switch to antihypertensive medication with a minimal impact on ARR (Table 4).

4. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes

ARR, aldosterone-to-renin ratio; MRA, mineralocorticoid receptor antagonist.

SUBTYPING

Imaging

Adrenal computed tomography (CT) and magnetic resonance imaging (MRI) are imaging techniques commonly used for assessing adrenal structures in patients with PA [25]. According to the Endocrine Society guidelines, adrenal CT scanning is mandatory before adrenal venous sampling (AVS) to exclude large masses that could be adrenocortical carcinoma and to assist interventional radiologists and surgeons where anatomically appropriate [68]. Although MRI is a valuable imaging tool, it is considered secondary to CT in PA due to its lower spatial resolution and higher costs [25]. Despite providing detailed images, MRI may fail to detect small adenomas and hyperplasia, which are crucial for PA subtyping. Patients with PA may exhibit a range of adrenal imaging features, including normal adrenal structures, unilateral adrenal limb thickening, unilateral microadenomas (less than 1 cm), unilateral macroadenomas (over 1 cm), and bilateral microadenomas or macroadenomas (or a mixture of both) [69]. APA may manifest as tiny hypodense nodules (generally less than 2 cm in diameter) on CT scans. Because large benign-appearing unilateral masses could be indicative of an adenoma that secretes both aldosterone and cortisol, dexamethasone suppression testing should be performed. Adrenal glands in IAH might appear normal on CT scans or show signs of nodular changes. Aldosterone-producing adrenal carcinomas are mostly larger than 4 cm in diameter, although smaller ones are occasionally found [70]. However, adrenal CT has some limitations. As adrenal adenomas become increasingly prevalent with age, the accuracy of CT imaging for subtyping PA decreases in patients of advanced age [71]. However, adenomas are less common in younger populations. Therefore, a small unilateral adenoma (typically less than 2 cm) found in a patient with PA is often misinterpreted as indicative of unilateral disease in this younger age group [71]. Moreover, CT scans do not provide insights into the secretion functionality of any identified nodules [72]. Multiple studies have demonstrated significant discordance between CT/MRI imaging and AVS in diagnosing PA [73]. For example an early Mayo Clinic study found that CT is accurate in only 53% of patients, potentially leading to 22% being wrongly excluded from surgery and 25% undergoing unnecessary or inappropriate surgery [74]. Similar findings have been reported in subsequent studies from Dallas and Nijmegen [75]. A meta-analysis of 950 patients also found a discordance between CT/MRI and AVS results in 37.8% of cases [76]. In a study involving 175 patients who underwent unilateral laparoscopic adrenal-

ectomy for PA, a significant discordance was noted between AVS and imaging methods, with MRI and CT results differing in 37.9% and 42.7% of patients, respectively, thereby reaffirming the Munich study's findings of the poor predictive value of these imaging techniques [77]. In line with the results of previous studies, CT and AVS showed discordant findings in 35.6% of in 466 PA patients from two tertiary centers in Korea [78]. This evidence underscores the indispensable role of AVS in diagnosing PA to prevent unnecessary or incorrect adrenalectomies.

Adrenal venous sampling

AVS is a diagnostic procedure performed to differentiate between unilateral and bilateral adrenal disease, particularly in PA [79]. Due to limitations of various imaging techniques in accurately differentiating these subtypes, AVS has remained the gold standard diagnostic tool [80]. Before performing AVS, it is necessary to discontinue the use of antihypertensive drugs that can disrupt the RAS, particularly those stimulating renin release [81]. Medications including loop and thiazide diuretics, amiloride, and MRAs should be withdrawn 4 weeks before AVS [82]. These medications are preferably replaced with antihypertensive drugs that exert less or minimal influence on renin secretion, such as α1-adrenergic receptor blockers and non-dihydropyridine long-acting calcium channel blockers (e.g., verapamil or diltiazem). If PRA or plasma renin concentration is suppressed, AVS can be conducted irrespective of the drug withdrawal timeline. Exceptionally, in cases where renin remains suppressed, MRA therapy can be maintained during the AVS procedure [65]. AVS is typically performed through a percutaneous approach via the femoral vein, utilizing fluoroscopy for guidance [83]. The left adrenal vein, which drains directly into the left renal vein, is often more straightforward to cannulate than the right adrenal vein. The right one is shorter and smaller, and it typically drains directly into the inferior vena cava. It is also not uncommon for the right adrenal vein to be invisible on adrenal CT or undetectable on adrenal venography because of adrenohepatic fusion [84]. Therefore, the success rate of AVS is lower in the right adrenal vein than in the left adrenal vein. However, AVS is a complex and costly procedure. Furthermore, it lacks a standardized procedure, leading to variations in success rates between medical centers, often dependent on the skill level of the interventional radiologist performing the procedure [73]. In the hands of skilled operators (usually found in high-volume PA centers treating over 30 patients annually), the technical success rate of AVS can exceed 90%. Despite the inherent complexity of this procedure, it is as-

sociated with a low complication rate (approximately 0.61%), with adrenal hemorrhage being the most severe yet rare complication [85]. Even when this occurs, it typically results in minor or no lasting impacts on adrenal function.

Performance of AVS

Simultaneous cannulation of the adrenal veins is a procedure proposed to mitigate fluctuations in aldosterone and cortisol secretion. This method aims to prevent any artificial alteration of the aldosterone production gradient between the two adrenal glands under basal conditions [73,86]. However, it is worth noting that this approach is invasive and demanding, requiring two catheter insertions, as opposed to a sequential technique. A recent retrospective study compared simultaneous and sequential AVS (with a 5-minute time gap between cannulations) under basal conditions and revealed no significant disparities in selectivity or lateralization indices [87]. Nevertheless, it remains unclear whether substantial time gaps, such as those that might occur during challenging cannulations, could significantly affect AVS results. It has been confirmed that, provided that the time between cannulation of the two adrenal veins remains relatively short, sequential cannulation exhibits comparable accuracy to simultaneous cannulation, even in an unstimulated procedure [73]. Considering the inconsistent evidence, the choice between the two methods is primarily determined by the radiologist's and/or the institution's preference [88]. Segmental AVS has been proposed for guiding selective nodulectomy, rather than complete adrenal resection, in PA patients [89]. This approach is crucial for surgically treating patients with bilateral APA or those with APA in the remaining gland after one-sided adrenal-ectomy. In segmental AVS, samples are taken from the central adrenal vein's tributaries to pinpoint the nodule's location within the gland. Despite its benefits, segmental AVS is technically demanding, time-consuming, and expensive. This procedure should only be undertaken at facilities with highly skilled radiologists due to its higher risk of complications than central AVS [90]. ACTH (1-24), a synthetic derivative of ACTH, is used during the AVS procedure. Two primary methods for administering ACTH (1-24) are performed: (1) continuous infusion of ACTH (1-24) (50 μg/hr, starting 30 minutes before the first sampling), and (2) a bolus injection of ACTH (250 μg [10 IU]) [25]. This approach can maximize the cortisol gradient, minimize aldosterone fluctuations, and enhance aldosterone production from an APA [74,82]. Steroidal prophylaxis is crucial for patients who have a high risk of allergic reactions. Similarly, those with subclinical hypercortisolism need careful management. Moreover, it is important to adjust protocols for AVS procedures that are not conducted in the early morning. ACTH (1-24) administration may benefit patients with bilaterally suppressed aldosterone production. It can also increase the success rate of adrenal cannulation in centers with low success rates. However, it may stimulate aldosterone secretion from the contralateral adrenal gland, reducing the lateralization index (LI). Given that there have been no reports of a change in lateralization from one side to the contralateral side after cosyntropin administration, the choice of the optimal procedure is determined by the individual patient's and/or center's preference and expertise [88].

Interpretation of AVS

Despite concerted efforts to standardize and harmonize AVS

Table 7. Definitions and Clinical Interpretations of Frequently Used AVS Indices

AVS index	Calculation	Cut-off values	Clinical interpretation
Selectivity index (SI)	$\dfrac{(Cortisol)_{AV}}{(Cortisol)_{PV}}$	≥2 or 3 (without cosyntropin)[a] >2 or 3 (preferable) without cosyntropin ≥5 (with cosyntropin) >3 or 5 (preferable) with cosyntropin	Successful cannulation of the adrenal veins
Lateralization index (LI)	$\dfrac{(Aldosterone/Cortisol)_{D-AV}}{(Aldosterone/Cortisol)_{ND-AV}}$	≥2 (without cosyntropin) ≥4 (with cosyntropin)	Significantly excess aldosterone secretion from D-AV compared with ND-AV
Contralateral ratio (CLR)	$\dfrac{(Aldosterone/Cortisol)_{ND-AV}}{(Aldosterone/Cortisol)_{PV}}$	<1	Significantly suppressed aldosterone secretion from ND-AV compared with PV
Ipsilateral ratio (ILR)	$\dfrac{(Aldosterone/Cortisol)_{D-AV}}{(Aldosterone/Cortisol)_{PV}}$	>2	Significantly excess aldosterone secretion from D-AV compared with PV (when CLR <1)

AVS, adrenal venous sampling; AV, adrenal vein; PV, peripheral vein; D-AV, dominant adrenal vein; ND-AV, non-dominant adrenal vein.
[a]Some centers consider a SI of 3 or higher as more reliable, while procedures with an SI between 2 and 3 should be performed with caution. The dominant adrenal vein corresponds to the adrenal gland producing excessive aldosterone, whereas the non-dominant adrenal vein is the adrenal vein from the opposite side.

interpretation, the cut-offs for interpretation criteria still vary across different centers [73,76,88]. Table 7 provides the definitions and clinical interpretations of commonly used AVS indices. The selectivity index (SI), an indicator of successful adrenal vein cannulation, has been reported to yield more reliable, accurate, and reproducible results when it is higher. Therefore, it is advisable to approach with caution those procedures where the SI falls below 2 for unstimulated procedures and less than 5 for stimulated ones [91]. The LI is utilized to localize the origin of aldosterone production. The ideal cut-off for determining patient eligibility for adrenalectomy remains inconsistent. It is likely that a gray area exists between unilateral and bilateral PA, especially in cases of asymmetrical bilateral conditions or when an APA coexists with bilateral aldosterone-producing cell clusters or cortical hyperplasia [92]. Historically, the LI cut-off for stimulated procedures was considered different from that for unstimulated ones, with a lower value suggested for the latter under basal conditions. Nevertheless, given the potential decrease in the LI during cosyntropin stimulation, a cut-off of 4 under both conditions rather than a lower LI for unstimulated procedures is generally recommended [88]. The contralateral ratio (CLR) is another parameter employed in AVS interpretation. Although it has been used as an auxiliary marker of unilateral PA, it does not appear to be a prerequisite for surgery [93]. It has been suggested that the CLR could be useful when the LI is in the gray zone, or when only the adrenal vein contralateral to an adrenal nodule is identified [93]. Several institutions have also suggested diagnosing unilateral PA with an ipsilateral ratio (ILR) above 2 and a CLR below 1 without using the LI [80]. In a retrospective study conducted in Korea, the importance of AVS parameters was examined in relation to postsurgical outcomes in 251 patients with PA [94]. It was found that a higher LI (≥10) was associated with an improved biochemical success rate (91.7%) compared to lower indices (66.7% for LI=3–4). Moreover, that study highlighted that for patients with an ILR >2, a CLR <0.25 was suitable for achieving biochemical success, and a CLR <1 was appropriate for clinical success. These findings further emphasize the critical role of these AVS indices in predicting surgical outcomes in PA patients.

OTHER STRATEGIES FOR SUBTYPING

Debates on the need to perform AVS
The Endocrine Society guidelines suggest that it might be possible to bypass AVS and proceed directly to unilateral adrenalectomy in patients who meet the following criteria: (1) age below 35

years; (2) a severe PA phenotype characterized by a PAC exceeding 30 ng/dL and spontaneous hypokalemia; and (3) a CT scan revealing a unilateral adenoma with a contralateral adrenal gland appearing normal [25]. Regarding the age criterion, two recent studies showed that imaging studies inaccurately predicted laterality in a significant number of patients 35 years or younger (two of 13 patients and two of 16 patients) [78,95]. According to results of the Subtyping Primary Aldosteronism: a Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial, treatment of PA based on either CT or AVS did not yield significant differences in patient outcomes after 1 year of follow-up [96,97]. The additional healthcare expenditures associated with AVS did not correspond to significant enhancements in patient quality of life, challenging the universal endorsement of AVS for all PA patients.

Functional imaging
Several functional imaging tests using tracers such as ^{11}C-metomidate, ^{18}F-CDP2230, and ^{68}Ga-pentixafor have been suggested for diagnosing the subtype of PA. However, none has demonstrated the necessary sensitivity or specificity to confidently direct PA patients towards unilateral adrenalectomy [98-100]. ^{11}C-metomidate positron emission tomography (PET)-CT scanning has been proposed as an alternative test for PA subtyping, offering 76% sensitivity and 87% specificity compared to AVS [98]. Metomidate can inhibit crucial enzymes in cortisol and aldosterone synthesis. Pre-procedure dexamethasone administration can enhance the contrast between APA and normal adrenal tissue [101]. However, its application is limited due to the need for an on-site cyclotron. A new tracer, ^{18}F-CDP2230, offers greater selectivity and a longer half-life without requiring dexamethasone pre-treatment, making it a promising alternative [100,102]. ^{68}Ga-pentixafor PET, which can diagnose PA with a sensitivity of 88% and a specificity of 100%, is based on the high expression of CXC chemokine receptor type 4 (CXCR4) in APAs, a factor associated with CYP11B2 expression [99, 103]. However, further studies with large samples are needed to confirm the efficacy of these methods in PA subtyping.

Steroid profiling
Steroid profiling is emerging as a promising new diagnostic tool in the decision-making process for managing PA [104]. The measurement of minor steroids (18-hydroxycorticosterone, [18OHB], 18-hydroxycortisol, [18OHF], and 18-oxo-cortisol, [18oxoF]) in the serum has been proposed as a way to distinguish PA subtypes. 18OHB is synthesized by aldosterone synthase from deoxycorti-

costerone as an intermediate during aldosterone biosynthesis and is secreted at a higher rate in patients with APA than in patients with bilateral adrenal hyperplasia (BAH). 18OHF and 18oxoF, also known as hybrid steroids, are synthesized by aldosterone synthase from 11-deoxycortisol; these two steroids are also present at higher concentrations in patients with APA than in patients with BAH and at very high concentrations in some familial forms of PA (FH-I and some families with FH-III) [82]. Additionally, a diagnostic technique that classifies various subtypes of adrenal tumors, which employs steroid profiling via LC/MS combined with machine learning algorithms, shows significant potential as a single-step solution [105].

COMORBIDITIES

Cardiometabolic complications

Conditions linked to obesity, such as metabolic syndrome, diabetes, and OSA, frequently coexist with PA. Several studies have identified a heightened incidence of metabolic syndrome and either insulin resistance or type 2 diabetes among PA patients [106,107]. Several theories have linked excessive aldosterone to these conditions. However, it remains uncertain whether the increased rate of cardiovascular diseases in PA patients compared to the rate in patients with essential hypertension is due to metabolic alterations. While the exact relationship between OSA and PA remains unclear, the 2016 Endocrine Society guidelines suggest screening all patients with hypertension and OSA for PA [25]. AF is a common complication in patients with PA, with studies showing that such patients face a risk of AF that is 12 times higher than those with essential hypertension [108]. A recent prospective study has found that 42% of patients with hypertension who were assessed for AF are diagnosed with PA, implying that AF is a frequent symptom of PA. It is well documented that hyperaldosteronism can induce heart structural issues such as inflammation, fibrosis, remodeling, hypertrophy, and functional and electrophysiological changes, all of which could lead to AF. Considering the association between adrenalectomy and a decreased risk of AF recurrence along with the risk reduction brought by MRA usage, it is advised that patients presenting with AF and hypertension without known arrhythmogenic causes should be screened for PA.

Renal complications

Patients with hyperaldosteronism are known to experience a swift progression of chronic kidney disease. PA can escalate the risk of renal disease through excessive activation of MRs. Harm-

ful renal effects of PA were initially reported by Halimi and Mimran [109], who found a higher rate of urinary albumin excretion adjusted for the estimated glomerular filtration rate (eGFR) in patients with PA than in those with primary hypertension. An analysis of 46 studies that compared renal function parameters between patients with PA and those with essential hypertension demonstrated a higher eGFR and more severe albuminuria in PA patients [110]. Following PA treatment, both medically and surgically treated patients exhibited decreases in eGFR and albumin excretion with an increase in serum creatinine. This indicates that renal dysfunction in patients with PA could be partially reversible. Given that aldosterone could potentially damage the entire renal tissue through MRs, patients with PA are recommended to receive early medical interventions using MRAs. This could help prevent irreversible renal injuries with a dose adequate for the task.

Bone complications

Experimental and clinical studies have provided evidence that hyperaldosteronism can lead to hypocalcemia and secondary hyperparathyroidism, resulting in a reduction in bone mineral density (BMD) and an elevated risk of fractures in patients with PA. Notably, patients with PA exhibit higher levels of serum parathyroid hormone (PTH) than patients with essential hypertension. Even with similar 25-hydroxyvitamin D levels, the surgical or pharmacological treatment of PA can lead to decreased PTH levels. Recent findings have indicated a higher prevalence of osteoporosis, a lower BMD, a poorer trabecular bone quality, and an increased incidence of vertebral fractures among patients with PA [111,112]. Reports have also suggested that the excessive secretion of aldosterone, as observed in conditions like PA, directly contributes to impaired muscle function [10]. Therefore, patients with PA should be aware of their heightened risk of low BMD and fractures.

TREATMENT

The goal of PA treatment is to normalize high BP and hypokalemia caused by aldosterone excess and reduce the risk of cardiovascular morbidity and mortality. The control of BP alone without effective blockade of aldosterone excess is insufficient for treating patients with PA [113]. Either unilateral adrenalectomy or MRA therapy can be effective in reducing the effect of excessive aldosterone and reversing cardiovascular morbidity [114]. In many studies, adrenalectomy was more effective than medical treatment for hypertension and hypokalemia [115,116]. In

addition, adrenalectomy could improve several quality of life indicators [117]. Evidence to date supports the preferential treatment of aldosterone excess by adrenalectomy. Medical treatment is recommended for patients with BAH without unilateral PA, a medical condition that cannot be treated surgically, or patients who are unwilling to undergo surgery. A limitation to establishing evidence for the recommendation is the lack of randomized controlled trials comparing the clinical efficacy of adrenalectomy and MRA treatment. Furthermore, improvements in hypertension or hypokalemia, but not cardiovascular outcomes, have been identified as primary endpoints in many studies [118,119].

Surgical treatment or percutaneous ablation in unilateral PA

Unilateral adrenalectomy with confirmed excessive aldosterone secretion is recommended as the treatment of choice for patients with unilateral PA (i.e., APA or UAH). Laparoscopic adrenalectomy is the first choice for surgery due to its low surgical risk and short hospital stay. In addition, there is a possibility of incomplete resection of aldosterone-secreting lesions. Percutaneous radiofrequency ablation is performed under local anesthesia and sedation with minimal skin incision [120]. This may be acceptable as an alternative for patients who are reluctant to undergo surgery and for those who are not eligible for a surgery due to their comorbidities. The biochemical remission rates of radiofrequency ablation in small retrospective non-randomized studies are 90% to 100% [121]. A multidisciplinary team that includes an endocrinologist, an experienced surgeon, an anesthesiologist, and an interventional radiologist should make final decisions on the best care.

Pathology

The immunohistochemical identification of aldosterone-producing lesions has been made possible using antibodies targeting CYP11B2, a crucial enzyme for aldosterone synthesis [122]. The degree of CYP11B2 expression is heterogeneous and correlated with the severity of PA [123]. The histopathology of primary aldosteronism (HISTALDO) consensus statement has delineated distinct pathological subtypes of unilateral PA, which encompass APA, solitary aldosterone-producing nodules or micronodules (APN or APM), multiple aldosterone-producing nodules or micronodules (MAPN or MAPM), and aldosterone-producing diffuse hyperplasia (APDH) (Table 8) [124]. The term "classical" histopathology in the context of unilateral PA typically refers to the presence of a single APA or APN. On the other hand, the term "non-classical" histopathology refers to the presence of MAPN, MAPM, or APDH. Patients with non-classical histopathological features of unilateral PA demonstrate a lower rate of biochemical success than those with classical features [125]. However, the clinical success rate is not significantly different between the two groups. Furthermore, the HISTALDO consensus statement cannot provide a histopathological diagnosis of bilateral PA because tissue samples of patients are usually unavailable since patients do not undergo surgery.

Perioperative management

Patients with PA have a high prevalence of resistant hypertension, hypokalemia, and cardiovascular complications [126,127]. Therefore, a medical evaluation and appropriate treatment are required before surgery to reduce the risks associated with general anesthesia and surgery. MRAs are recommended as the first-line drugs to control hypertension and hypokalemia before adrenalectomy [25]. Other antihypertensive medications and

Table 8. HISTALDO Consensus for Histopathology in Unilateral Primary Aldosteronism

Histopathological entity	Neoplastic lesion	Classical/ Non-classical	Visible in H&E stain	CYP11B2 (+) lesion maximal size
Aldosterone-producing adrenocortical carcinoma (APACC)	Neoplastic	Classical	Visible	≥10 mm
Aldosterone-producing adenoma (APA)	Neoplastic	Classical	Visible	≥10 mm
Aldosterone-producing nodule (APN)	Non-neoplastic/hyperplastic	Classical	Visible	<10 mm
Aldosterone-producing micronodule (APM)[a]	Non-neoplastic/hyperplastic	Non-classical	Invisible	<10 mm
Multiple APN or APM	Non-neoplastic/hyperplastic	Non-classical	Visible or invisible	<10 mm, multiple
Aldosterone-producing diffuse hyperplasia (APDH)	Non-neoplastic/hyperplastic	Non-classical	Invisible	≥50% in zona glomerulosa

Modified from Williams et al. [124], with permission from Oxford University Press.
HISTALDO, histopathology of primary aldosteronism; H&E, hematoxylin-eosin; CYP11B2, aldosterone synthase.
[a]Formally known as aldosterone-producing cell clusters.

EnM

potassium supplements might be required. After surgery, transient hypotension, hyperkalemia, and a decrease in the eGFR might occur after adrenalectomy [128,129]. Therefore, it is necessary to monitor BP, electrolytes, and serum creatinine. MRAs and potassium supplements should be discontinued to avoid hyperkalemia in the first postoperative day [25]. In addition, dose reduction or discontinuation of other antihypertensive drugs might be required [130]. Hyperkalemia may be transient or prolonged after surgery. Thus, fluids should be used in normal saline without potassium chloride unless the serum potassium level is very low (i.e., <3 mmol/L) [25]. A decreased eGFR after surgery is a predictive indicator of postoperative hyperkalemia [131]. However, a decreased eGFR in the early postoperative period may indicate a good prognosis for long-term renal function [132].

Medical treatment in BAH or when the identification of unilateral PA fails

An MRA alone or in combination with other antihypertensive agents is recommended for patients with BAH, patients whose unilateral PA cannot be identified, patients who have a medical condition that cannot be treated surgically, and patients who are unwilling to undergo surgery. MRAs can normalize hypertension and hypokalemia and independently reduce target organ damage [48]. The insufficient inhibition of excessive aldosterone action due to inadequate MRA doses may increase cardiovascular risk [133]. The control of BP, normalization of potassium, and resolution of plasma renin suppression (PRA ≥1 µg/L/hr) can be used as indicators for administering an adequate MRA dose [134,135]. Spironolactone is the first-recommended and the only available MRA in Korea. MRAs can induce gynecomastia and erectile dysfunction in a dose-dependent manner in men due to its antiandrogen and progesterone-like effects [136]. Eplerenone is a selective MRA that has lower efficacy than spironolactone. However, it has no antiandrogen or progesterone agonistic effects. Thus, it can be a useful alternative in patients experiencing those side effects [137,138]. It has not been approved by the U.S. Food and Drug Administration or European Medicines Agency for treating PA. It is currently not available in Korea.

Amiloride is a potassium-sparing diuretic that can control hypertension and hypokalemia without sex steroid-related side effects [139]. It is available in Korea. It can also be used as an alternative to spironolactone for patients experiencing side effects. Finerenone, which is used for treating chronic kidney disease in patients with type 2 diabetes, is the only novel non-steroidal

MRA currently available in the United States. Finerenone may be a potential option for PA without the side effects of traditional MRAs [140]. Although the BP-lowering effect was insignificant in studies of patients with diabetic kidney disease, this may be because the participants did not have PA, and the dose was insufficient for the BP-lowering effect [140]. Recently, esaxerenone showed a favorable efficacy and safety profiles in Japanese patients with hypertension and PA [141]. Baxdrostat, a selective aldosterone synthase inhibitor, showed substantial reductions in BP in patients with treatment-resistant hypertension [142].

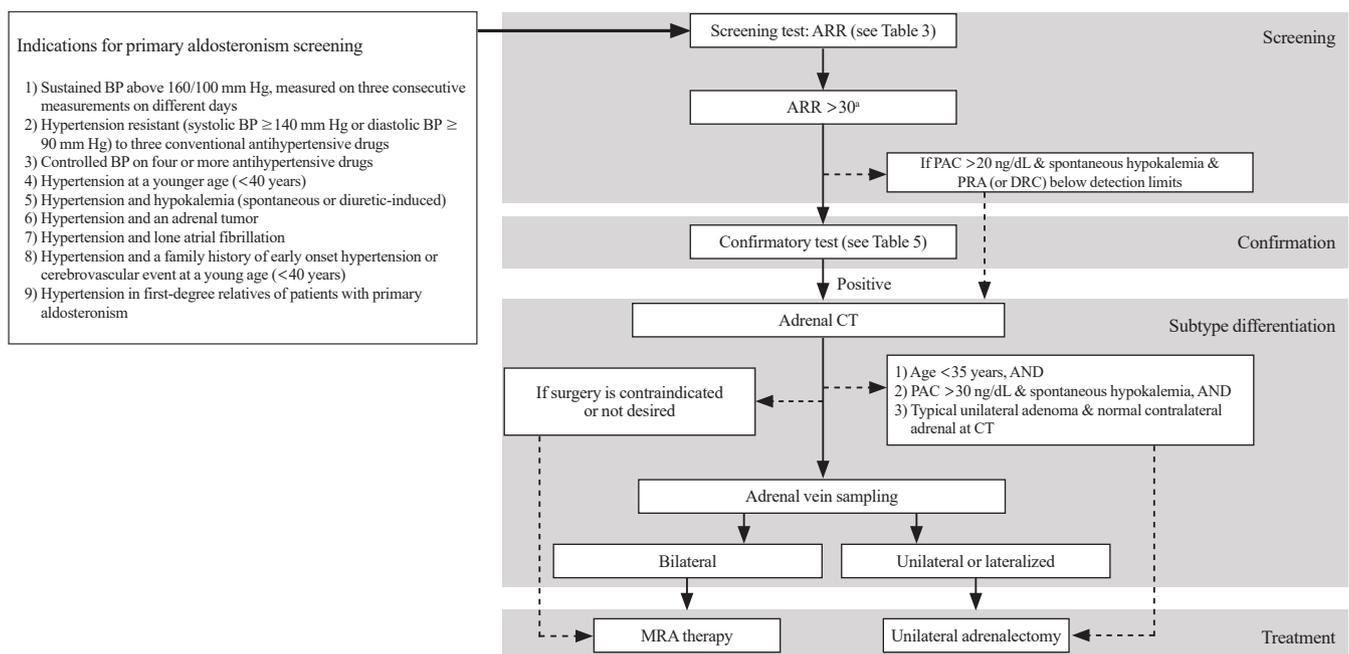### Special consideration for females with PA who are pregnant or desire childbearing

There are no formal recommendations for management in pregnant women with PA. Women with unilateral PA should undergo adrenalectomy before planning pregnancy. The diagnosis of PA during pregnancy relies primarily on biochemical methods to measure low renin activity and high aldosterone concentrations in the blood due to physiological changes and contraindications to testing for confirmation and localization. The goals of management are to correct BP and hypokalemia and prevent hypertension-related maternal and fetal morbidity and mortality [143]. Hypertension is treated with approved antihypertensive drugs in pregnant women (α-methyldopa, hydralazine, labetalol, and nifedipine are only used after 20 weeks of pregnancy) [144]. However, although exposure to medication in the first trimester raises concerns about structural malformations, any use of these agents in pregnant women should be approached with caution. This is because the fetal central nervous system, which develops throughout pregnancy, can be influenced by exposure at any stage [145]. Hypokalemia is corrected with potassium supplements. However, for patients who do not respond to these conservative treatments, an MRA may be considered when the benefits of treatment are expected to outweigh the risks. Spironolactone is contraindicated in pregnant women and those who desire to be pregnant due to the lack of evidence on its safety in controlled trials [144]. The anti-androgenic effect of spironolactone can potentially interfere with sexual development. However, some reports have shown that eplerenone and amiloride can be safely used in several pregnant women without afferent side effects [146]. Therefore, eplerenone and amiloride can be considered carefully in cases of persistent resistant hypertension and hypokalemia despite the appropriate use of conventional antihypertensive drugs [146]. Furthermore, if PA due to unilateral adrenal adenoma is strongly suspected due to spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal

cortical adenoma on MRI, surgery may be considered after the second trimester if resistance to medical treatment occurs [146].

FOLLOW-UP STRATEGY AFTER SURGERY

Biochemical and clinical parameters should be monitored to assess the effectiveness of surgery in patients who undergo adrenalectomy. PRA and PAC should be measured to evaluate biochemical responses. Measurements of PRA and PAC shortly after surgery may also be helpful as early signs of biochemical responses, although suppression of renin activity does not immediately recover. PRA and PAC should be measured to evaluate biochemical remission at least 1 month and 6 months after surgery. The biochemical remission rate of unilateral adrenalectomy in patients with unilateral PA under successful AVS guidance is almost 100% [15,147]. Biochemically persistent aldosterone excess should consider the possibility of determination failure of unilateral PA (either bilateral or contralateral disease), failure of complete surgical removal, and, very rarely, recurrence of aldosterone-producing carcinoma [48]. Conversely, persistent hypoaldosteronism requiring mineralocorticoid replacement therapy (fludrocortisone) due to permanent suppression of aldosterone secretion from the contralateral adrenal gland can occur in up to 5% of patients undergoing adrenalecto-

my [131]. BP usually maximally improves within 1 to 6 months after surgery. However, it may continue to decrease for up to 1 year in some patients [25]. Therefore, BP should be monitored to determine whether a dose reduction or discontinuation of antihypertensive medications is needed. Conversely, hypertension may persist despite biochemical remission because BP is a highly complex phenotype. It can be elevated independently of preexisting essential hypertension or other medical conditions that may affect BP. A meta-analysis has shown that the clinical remission rate after unilateral adrenalectomy is about 50% [148]. Persistent hypertension does not indicate treatment failure. Hypertension in patients with biochemical remission can be appropriately treated with antihypertensive agents other than MRAs. A shorter duration of hypertension, fewer antihypertensive drugs before surgery, younger age, female sex, higher eGFR, and lower body mass index are favorable prognostic factors for clinical remission. The Primary Aldosteronism Surgical Outcome score using six preoperative factors (known duration of hypertension, sex, antihypertensive medication dosage, body mass index, target organ damage and size of largest nodule at imaging) can be a useful predictive tool [149,150]. Moreover, patients who have been treated for PA could face a heightened risk of new-onset AF for up to 3 years. Consequently, post-treatment monitoring for AF, particularly following adrenalectomy,

Fig. 1. Suggested diagnostic process for patients with primary aldosteronism. BP, blood pressure; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity; DRC, direct renin concentration; CT, computed tomography; MRA, mineralocorticoid receptor antagonist. [a]Consider using PAC >15 ng/dL as a screening cutoff if the renin level is excessively suppressed.

may be essential during this period [151].

CONCLUSIONS

Despite its relatively high prevalence, PA often remains under-diagnosed and undertreated, leading to unnecessary cardiovascular morbidity and mortality. This Korean consensus statement provides a comprehensive and detailed overview of diagnostic and treatment strategies for PA based on the latest available scientific evidence and expert consensus. Fig. 1 depicts a diagnostic process for PA clinical practice based on the 2023 guideline. The adoption of the guideline into clinical practice is expected to raise awareness, improve the accuracy of diagnoses, and ensure appropriate treatment for patients suffering from this condition. Through a commitment to patient-centered care, evidence-based practice, and ongoing research, we strive to reduce the burden of PA in Korea and improve the health and well-being of our patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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