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OPINION

Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021

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Abstract. Primary aldosteronism (PA) is associated with higher cardiovascular morbidity and mortality rates than essential hypertension. The Japan Endocrine Society (JES) has developed an updated guideline for PA, based on the evidence, especially from Japan. We should preferentially screen hypertensive patients with a high prevalence of PA with aldosterone to renin ratio ≥200 and plasma aldosterone concentrations (PAC) ≥60 pg/mL as a cut-off of positive results. While we should confirm excess aldosterone secretion by one positive confirmatory test, we could bypass patients with typical PA findings. Since PAC became lower due to a change in assay methods from radioimmunoassay to chemiluminescent enzyme immunoassay, borderline ranges were set for screening and confirmatory tests and provisionally designated as positive. We recommend individualized medicine for those in the borderline range for the next step. We recommend evaluating cortisol co-secretion in patients with adrenal macroadenomas. Although we recommend adrenal venous sampling for lateralization before adrenalectomy, we should carefully select patients rather than all patients, and we suggest bypassing in young patients with typical PA findings. A selectivity index ≥5 and a lateralization index >4 after adrenocorticotropic hormone stimulation defines successful catheterization and unilateral subtype diagnosis. We recommend adrenalectomy for unilateral PA and mineralocorticoid receptor antagonists for bilateral PA. Systematic as well as individualized clinical practice is always warranted. This JES guideline 2021 provides updated rational evidence and recommendations for the clinical practice of PA, leading to improved quality of the clinical practice of hypertension.

Key words: Primary aldosteronism, Guideline, Screening, Confirmatory test, Adrenal venous sampling

Introduction

Primary aldosteronism (PA) is a major cause of curable hypertension and is highly prevalent in patients with hypertension, a cause of resistant hypertension, and closely associated with target organ damage [1-3]. Appropriate diagnosis and treatment of PA are thus important in the daily clinical practice of hypertension. The Endocrine Society has published clinical practice guidelines [4], followed by various academic societies [5-8]. The establishment of a clinical practice guideline following various activities of medical associations and academic societies have contributed to a substantial improvement in the clinical practice of hypertension and PA in Japan. However, it is essential to revise the guideline periodically to reflect the updated evidence [9]. More importantly, evidence from Japan should be incorporated, considering the framework of the medical insurance system in Japan. Much evidence has accumulated in Japan during the last six years. In particular, the multi-center clinical studies named the Japan Primary Aldosteronism Study (JPAS) and the Japan Rare/Intractable Adrenal Diseases Study (JRAS), mainly supported by the Japan Agency of Medical Research and Development (AMED), have created a large-scale PA registry and provided much evidence unique to Japan. From such a background, the PA guideline task force of the Japan Endocrine Society has developed a new clinical practice guideline for PA. We systematically generated a series of clinical answers to major clinical questions (CQs). We made appropriate recommendations for the diagnosis and treatment of PA, utilizing as much evidence as possible from Japan and based on the medical insurance system in Japan.

Methods

Purpose

This clinical practice guideline aims to improve and standardize PA clinical practice in Japan by summarizing the answers to major CQs of PA medical care, presented as points, and providing the certainty of the evidence and strength of the recommendations.

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Abbreviations: ACE, Angiotensin converting enzyme; ACTH, Adrenocorticotropic hormone; APA, Aldosterone-producing adenoma; ARB, Angiotensin type 1 receptor blocker; ARC, Active renin concentration; ARR, Aldosterone to renin ratio; AVS, Adrenal venous sampling; BMI, Body mass index; CIN, Contrast-induced nephropathy; CKD, Chronic kidney disease; CLEIA, Chemiluminescent enzyme immunoassay; CQ, Clinical question; CR, Contralateral ratio; CT, Computed tomography; CYP, cytochrome; eGFR, Estimated glomerular filtration rate; EH, Essential hypertension; EPL, Eplerenone; ESA, Esaxerenone; FH, Familial hyperaldosteronism; JPAS, Japan Primary Aldosteronism Study; LC-MS/MS, Liquid chromatography–tandem mass spectrometry; LI, Lateralization index; MDCT, Multidetector row computed tomography; MRA, Mineralocorticoid receptor antagonist; MRI, Magnetic resonance imaging; PA, Primary aldosteronism; PAC, Plasma aldosterone concentrations; PPV, Positive predictive value; PRA, Plasma renin activity; RIA, Radioimmunoassay; SI, Selectivity index; SPECT, Single photon emission computed tomography; SPL, Spironolactone

Basic concept of the revision

We have revised the guideline based on the 2016 Consensus statement on the treatment of PA in Japan of the Japan Endocrine Society [6] and prepared with consideration of the following points:

1) Consistency with the 2019 guideline for the management of hypertension by the Japanese Society of Hypertension [7]

2) Utilization of evidence unique to Japan, in particular, that from the clinical studies by the JPAS and JRAS study groups of the AMED

3) Collaboration with related academic societies engaged in PA and hypertension treatment (the Japanese Society of Hypertension, the Japanese Society of Nephrology, the Japan Association of Endocrine Surgeons, and the Japan Society for the Study of Hypertension in Pregnancy) and the research program on rare and intractable diseases of the Ministry of Health, Labor, and Welfare, Japan, and of the National Center for Global Health and Medicine, Japan

The task was one of the important clinical issues of the Japan Endocrine Society. The target readers of the current guideline are all physicians engaged in hypertension and public health nurses, dietitians, and pharmacists. All task force members are specialists in endocrine and metabolic diseases, hypertension, and renal diseases engaged in PA medical care and approved by the Japan Endocrine Society.

Method of preparation

The preparation process followed the stipulations of the MINDS Manual for Guideline Development 2017 (Tokyo: Japan Council for Quality Health Care, 2017). Major CQs were selected using PICO followed by a reference search, the creation of abstract format and abstract tables, and the creation of recommendations with the certainty of evidence and strength of recommendations. We have selected the literature used for the guideline *via* two steps: primary screening by a systematic review process developed by the International Medical Information Center (IMIC) EBM (Evidence-Based Medicine) Research Center (Tokyo, Japan) and secondary screening by members of the systematic review committee based on various objective criteria and critical review of the literature.

Determination of the evidence quality and strength of recommendation

The certainty of evidence and strength of recommendations were determined based on the MINDS Manual for Guideline Development 2017 and graded as shown in Tables 1 and 2.

Consensus and approval process

Consensus on the CQs, recommendations, certainty of evidence and strength of the recommendations, and commentary on the recommendations were determined primarily by the modified Delphi consensus methods and multiple email communications, mainly because of the COVID-19 pandemic, in addition to one face-to-face task force meeting. This consensus process was effective in ensuring scientific objectivity and excluding various biases. In addition, the drafts compiled by the task force were reviewed by the Committee of the Clinically Important Issues and the Peer Review Committee of the Japan Endocrine Society (Chairman, Hiroaki Masuzaki, University of the Ryukyus), which were comprised of members of the related academic societies and city hospitals, as well as clinicians and external advisors. In addition, the revised version was provided to public comments on members of the Japan Endocrine Society. After revising the guideline by incorporating the comments as appropriate, the Japan Endocrine Society finally approved the guideline.

Table 1 Certainty (strength) of the evidence level as a whole

Strength	Explanation
A (strong)	Confidence that the estimated effects support the recommendations is strong
B (medium)	Confidence that the estimated effects support the recommendations is moderate
C (weak)	Confidence that the estimated effects support the recommendations is limited
D (very weak)	Confidence that the estimated effects support the recommendations is uncertain

Table 2 Strength of the recommendations

Recommendation level	Explanation
1	It is recommended to “implement” or “not implement”
2	It is suggested to “implement” or “not implement”

Funding source

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Disclosure and management of conflicts of interest (COI)

COI associated with the chairperson and all task force members were disclosed following the Japan Endocrine Society's common guidelines for COI in clinical research and listed at the end of the guideline. We have implemented appropriate COI management following guidelines on eligibility criteria for formulating clinical practice guidelines (Conflicts of Interest Committee, the Japanese Association of Medical Sciences, March 2017).

Clinical Questions

General remarks

CQ 1. What is PA?

Point 1. PA is a major cause of secondary hypertension induced by autonomous aldosterone secretion from the adrenal glands (A).

Point 2. We recommend adequate diagnosis and specific treatment according to the clinical guidelines for PA (1A).

Evidence and comments

PA is a disease involving hypersecretion of aldosterone from the adrenal glands, first described by Conn JW in 1955 [1] and a major cause of secondary hypertension. The pathogenic mechanism of PA consists of autonomous aldosterone hypersecretion inducing sodium reabsorption and potassium excretion from the kidney, followed by intravascular volume expansion. It is characterized by hypertension, hypokalemia, and renin suppression. The prevalence of cerebrovascular and cardiovascular complications such as stroke, left ventricular hypertrophy, atrial fibrillation, coronary artery disease, and heart failure are higher in PA patients than those with essential hypertension (EH) [10, 11]. In a meta-analysis, patients with PA had increased risks of stroke (odds ratio [OR] 2.58), coronary artery disease (OR 1.77), atrial fibrillation (OR 3.52), and heart failure (OR 2.05), as well as diabetes (OR 1.33), metabolic syndrome (OR 1.53), and left ventricular hypertrophy (OR 2.29), compared with patients with EH [12]. Therefore, appropriate diagnosis and treatment according to the clinical guidelines for PA are recommended [6, 7]. Also important is an individualized medicine respecting patients' desire not for further investigation and selecting medical treatment after enough informed consent of the disease.

CQ 2. How prevalent is PA in patients with hypertension?

Point 1. The prevalence of PA in patients with hypertension is reportedly 3–12% in primary care centers and 5–29% in referral centers (B).

Evidence and comments

The reported prevalence of PA in patients with hypertension has ranged widely because of differences among studies in patient selection, screening procedures, hormonal assays, confirmatory test type, and the associated cut-off values. However, since clinical practice guidelines recommended screening for PA using plasma aldosterone concentrations (PAC) and plasma renin activity (PRA), the prevalence of PA has increased: 3.8–12.7% in primary care centers and 5.6–29.8% in referral centers, respectively [13-15]. It has been reported that the prevalence of PA is higher in patients with severe hypertension (high-normal blood pressure, 5.5%; stage 1, 4.2%; stage 2, 10.2%; stage 3, 16.4%) [13] or hypokalemia (28.1% *vs.* 4.3% with normokalemia) [15]. Although the number of new diagnoses of PA has been increasing every year in Japan after the publication of guidelines [5, 6], most of the patients are bilateral PA [16, 17].

CQ 3. Are the prevalence of cerebral, cardiovascular, and chronic kidney diseases higher in patients with PA than in those with EH?

Point 1. The prevalence of cerebral and cardiovascular diseases and renal complications such as stroke, left ventricular hypertrophy, atrial fibrillation, coronary artery disease, heart failure, and proteinuria are higher in PA patients than in those with EH (B).

Point 2. A high PAC, hypokalemia, the unilateral subtype, and autonomous cortisol co-secretion contribute to cerebral and cardiovascular diseases and renal complications (B).

Point 3. The rates of obesity, impaired glucose tolerance,

and sleep apnea syndrome are higher in patients with PA than those with EH (B).
EH: essential hypertension

Evidence and comments

The prevalence of cerebral and cardiovascular diseases and renal complications such as stroke, left ventricular hypertrophy, atrial fibrillation, coronary artery disease, heart failure, and proteinuria are higher in patients with PA than in those with EH after adjusting for age and blood pressure [11, 18]. In a PA database established by the JPAS, the overall prevalence of cerebral and cardiovascular diseases was 9.4% (stroke, 7.4%; ischemic heart disease, 2.1%; heart failure, 0.6%; and atrial fibrillation, 2.8%) in 2,582 patients with PA with an average age of 53.2 years and average blood pressure of 141.4/86.5 mm Hg, and this prevalence was significantly higher than that in age-, sex-, and blood pressure-matched patients with EH [11]. Especially, a high PAC (≥125 pg/mL), hypokalemia, and the unilateral subtype significantly increased the adjusted odds ratios for cerebral and cardiovascular diseases [11]. In addition, the rates of left ventricular hypertrophy are higher in patients with PA than in patients with EH [12]. In JPAS, PAC, as determined by the captopril challenge test (CCT) or saline infusion test (SIT), and hypokalemia significantly correlated with the left ventricular mass index, which significantly improved 6–12 months after medical or surgical treatment [19]. In contrast to the patients with high PAC, one study demonstrated no significant difference in the risk of cardiovascular events between the PA patients with normal PAC and EH [20]. Furthermore, patients with adrenal adenomas co-secreting aldosterone and cortisol had higher cardiovascular complications rates than those with aldosterone-producing adenomas (APA) [21].

The prevalence of renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or proteinuria defined as a +, ++ or +++ result on the dipstick test) was reported as 19.7%. The prevalence of proteinuria was significantly higher in PA patients than those with EH with similar age and blood pressure. A high PAC and hypokalemia significantly increased the odds ratio of the renal impairment in patients with PA compared to the age-, sex-, and blood pressure-matched patients with EH [18]. In a meta-analysis, patients with PA had a high eGFR and high prevalence of albuminuria compared to non-PA hypertensive patients, and MRAs and adrenalectomy contributed to an improvement in the eGFR and albuminuria in the PA patients [22]. In addition, PAC was reportedly higher in PA patients with renal impairment than in those without it [18]. Furthermore, higher urinary albumin excretion and hypokalemia at the first visit were predictors of a decreased eGFR after specific treatment of PA [23], and the sharper the decrease in the eGFR at the early stage MRAs treatment, the milder the decrease after the treatment [24].

The JPAS demonstrated that the prevalence of diabetes mellitus in PA patients was 21.6%, higher than that in age- and sex-matched patients with EH or in the general population [25]. In a meta-analysis, the risks of metabolic syndrome and diabetes mellitus were significantly higher in patients with PA than in patients with EH [12]. The prevalence of sleep apnea syndrome was 67.6% in patients with PA [26].

Screening

CQ 4 What hypertensive patients should be screened for PA?

Point 1. We recommend screening all hypertensive patients for PA, especially those with a high prevalence of PA (1B).
Point 2. Clinical features suspicious of PA include spontaneous hypokalemia, resistant hypertension, hypertension onset before 40 years of age, adrenal tumor, stroke at a young age, and sleep apnea syndrome (C).

Evidence and comments

Although the typical features of PA are hypertension and hypokalemia, recent studies have demonstrated normal serum potassium concentrations in many PA patients with the spread of screening [27]. Since PA patients have a high risk of cardiovascular and renal complications [10, 11], we recommend PA screening in all hypertensive patients, especially those with clinical features suspicious of PA. Recent studies have reported that screening for PA is cost-effective compared with continuing medication in patients with resistant hypertension [28, 29].

Spontaneous hypokalemia, resistant hypertension, hypertension onset before 40 years of age, high blood pressure (>150/100 mmHg), presence of adrenal tumors on CT, stroke at a young age, and sleep apnea syndrome are as features of hypertensive patients suspicious of PA [4, 27, 30-32] (Table 3). The cut-off blood pressure for PA was changed from >160/100 mmHg [6, 7] to >150/100 mmHg according to the Endocrine Society guideline [4]. Screening for PA is recommended more strongly in cases of pediatric hypertension because the prevalence of type I familial hyperaldosteronism is high and not always accompanied by hypokalemia [33, 34].

CQ 5. How do we screen PA?

Point 1. We recommend using the PAC measured by the CLEIA*[1] as a reference for diagnosing PA (1A).
Point 2-1. We recommend judging the screening test positive when ARR (PAC/PRA ratio) ≥200 and PAC ≥60 pg/mL (2C). We recommend judging the screening test is

Table 3 Subgroups with a high prevalence of primary aldosteronism in hypertensive patients

1	Hypokalemia (including diuretic-induced)
2	Resistant hypertension
3	Onset of hypertension before age 40 years
4	Untreated blood pressure ≥150/100 mmHg
5	Adrenal tumors
6	Onset of stroke at a young age
7	Sleep apnea syndrome

provisionally positive when ARR is between 100–200 set as a borderline range and PAC ≥60 pg/mL until the PAC by CLEIA is generalized and its optimal cut-off established. For those patients with provisionally positive screening, we recommend that the subsequent medical management, including the confirmatory test, is individualized, considering the patient's desire, age, and clinical findings, including the presence of hypokalemia and adrenal tumors on CT (2C). In contrast, PA is not completely excluded even with negative screening results (2C).

Point 2-2. When the ARC is measured instead of PRA, we recommend judging the screening test positive when ARR (PAC/ARC ratio) ≥40 and PAC ≥60 pg/mL (2D). We recommend judging the screening test is provisionally positive when ARR (PAC/ARC ratio) is between 20 to 40 set as a borderline range and PAC ≥60 pg/mL and subjected to the same individualized management as in Point 2-1 (2D).

Point 3. Although it is desirable to conduct blood sampling early in the morning in the supine position after overnight fasting, that obtained at any time in the sitting position is acceptable for screening (2C).

Point 4. We recommend switching anti-hypertensive medicines to calcium channel blockers, alpha-blockers, or combinations (2C) to avoid false-positive and false-negative results. However, appropriate medical treatment of hypertension and hypokalemia should always prioritize screening tests (1B).

*1 The assay methods of PAC were changed from RIA to CLEIA. PAC measured by CLEIA was shown to be almost equivalent to that measured by LC-MS/MS.

ARC, active renin concentration; PRA, plasma renin activity

Evidence and comments

Since April 2021, RIA kits for PAC (SPAC-S Aldosterone kits) have no longer be available for use in Japan and have been replaced entirely by CLEIA [35-40]. Since the CLEIA kits show good traceability to certified reference materials of aldosterone (NMIJ CRM 64026402, the National Metrology Institute of Japan) and good correlation with LC-MS/MS results, we recommend using PAC by CLEIA for the diagnosis of PA. The characteristics of the CLEIA methods for PAC measurement and their comparison with the conventional RIA method are in Table 4. Since PAC by CLEIA became lower than by the RIA, cut-off values for the screening and confirmatory tests needed reconsideration.

To screen for PA, the aldosterone to renin ratio (ARR) has been commonly used [30, 41-43] with a cut-off value ranging from 200 to 400 (PAC [pg/mL]/PRA [ng/mL/h]) among countries. Although it is necessary to review the ARR cut-off value according to the change in the assay method of PAC, the conventional cut-off value of 200 (pg/mL/ng/mL/h) by RIA is significantly lower than that in other countries. The values by RIA do not meet the LC-MS/MS equivalent values as the international standard. We thus have kept the same ARR cut-off value of 200 by CLEIA as a requirement for positive screening. However, the ARR of 200 by RIA is almost equivalent to 100 by CLEIA. Therefore, we designated ARR in the borderline range from 100–200 by CLEIA as provisionally positive. ARC instead of PRA has been alternatively used to evaluate renin [44-46]. Although it is difficult to convert ARC to PRA, ARR (PAC/ARC) ≥40 was defined as positive results for convenience. In addition, following PAC/PRA, we also designated ARR (PAC/ARC) in the borderline range from 20 to 40 as provisionally positive.

The ARR is strongly affected by its denominator, PRA; even a low PAC may lead to positive screening results [47, 48]. Therefore, to avoid false-positive results, combining PAC (*i.e.*, ≥150 pg/mL in Mayo Clinic [41], ≥120 pg/mL in Japan [6, 7]) with ARR ≥200 has been advocated as the screening criteria. In addition, the patients with higher PAC (PAC [RIA] >125 pg/mL by the JPAS [11]; PAC [RIA] >160 pg/mL by one single-center study [20]) were associated with a higher prevalence of cardiovascular events than those with normal PAC. The PAC of 120 pg/mL by RIA, which has been used as the PAC cut-off, corresponded to 48.5 pg/mL by the LC-MS/MS [38] and 54.6 pg/mL [37], 58.1 pg/mL [39], and 66.2 pg/mL [35], respectively, by the CLEIA. In addition, the cut-off value of PAC in the SIT is 60 pg/mL by CLIEA [49]. Taking all these together, we recommended using a PAC ≥60 pg/mL as the cut-off of PAC to combine with ARR ≥200 for the positive screening test.

We recommend judging the screening test positive when ARR (PAC/PRA) ≥200 or ARR (PAC/ARC) ≥40 and PAC ≥60 pg/mL. The screening test is also designated to be provisionally positive when ARR (PAC/PRA) between 100–200 or ARR (PAC/ARC) ≥between 20 to 40 and PAC ≥60 pg/mL until the PAC by CLEIA is

Table 4 Characteristics of the CLEIA methods for PAC measurement and their comparison with the conventional RIA method

Product name	Lumipulse Presto Aldosterone/ Lumipulse G Aldosterone	Accuraseed Aldosterone·S	Determiner CL Aldosterone
Manufacturer	FUJIREBIO INC.	FUJIFILM Wako Pure Chemical Corp.	Minaris Medical Co., Ltd.
Principle of measurement	CLEIA	CLEIA	CLEIA
Reference material for calibration (NMIJ CRM 6402)*1	Yes	Yes	No
Expression value of the kit	Equivalent to LC-MS/MS	Equivalent to LC-MS/MS	Equivalent to RIA (Conversion formula from CLEIA to LC-MS/MS: Y = 0.78X)*5
Conversion formula from CLEIA (X) to RIA (Y) (pg/mL)	Y = 1.174X + 42.3*2 Y = 1.61X + 31.9*4	Y = 1.307X + 44.1*3	Y = 1.0X + 42.3*5
Conversion formula from RIA (X) to CLEIA (Y) (pg/mL)	Y = 0.852X – 36.0*2 Y = 0.62X – 19.8*4	Y = 0.765X – 33.7*3	Y = 1.0X – 42.3*5
CLEIA values corresponding to 120 pg/mL by RIA*6	66.2 pg/mL*2 54.6 pg/mL*4	58.1 pg/mL	77.7 pg/mL
CLEIA values corresponding to 60 pg/mL by RIA*6	15.1 pg/mL*2 17.4 pg/mL*4	12.2 pg/mL	17.7 pg/mL

The contents are based on the published data in the cited reference and the materials of the manufactures (as of May 30, 2021)
*1 Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp/)
*2 Setting by the manufacturer based on Ref. 35 (Nishikawa T, *et al.*)
*3 Ozeki Y, *et al.* (Ref. 39)
*4 Teruyama K, *et al.* (Ref. 37)
*5 Nishikawa T, Kuwa K (Ref. 40)
*6 Conversion using the conversion formula from RIA (X) to CLEIA (Y) shown in the 3rd row from the bottom.

generalized and its optimal cut-off established. We recommend individualized medical management considering the patient's desire, age, and clinical findings (hypokalemia, adrenal tumors on CT, *etc*.) in patients with provisionally positive screening. It is necessary to optimize the cut-off value of ARR by CLEIA and the medical management policy of the patients where the judgment of ARR differs between the RIA and CLEIA by accumulating further evidence. However, it should be noted that PA is not completely excluded even with negative screening results.

Since PAC and PRA are affected by blood collection conditions, we recommend collecting blood early in the morning in the supine position after overnight fasting [50]. However, it may be difficult to adhere to the desired conditions in daily clinical practice strictly. Simple blood sampling in the sitting position is acceptable for the first measure of screening, and we recommend blood sampling under more stringent requirements is as needed.

Many antihypertensive medicines affect renin and aldosterone concentrations. Beta-blockers may cause false-positive results by suppressing renin [51, 52], whereas diuretics may yield false-negative results by elevating renin. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blockers (ARBs), and calcium channel blockers tend to induce false-negative results [50], but the effects are not clinically significant [45]. Alpha-blockers do not affect renin or aldosterone concentrations [22]. However, in typical PA, these antihypertensive medicines do not affect the screening results [53] or the subtype testing [54]. We recommend switching antihypertensive drugs to calcium channel blockers, alpha-blockers, and combinations to avoid false-positive and false-negative results. ACE inhibitors and ARBs are also acceptable for screening as appropriate. Treatment of hypertension is always a priority over screening tests.

Confirmatory tests

CQ 6. How do we confirm aldosterone hypersecretion?

Point 1. We recommend the confirmatory tests to prove autonomous aldosterone hypersecretion and to exclude false-positive screening results (1B).

Point 2. A definitive clinical diagnosis of PA requires one positive confirmatory test (1C). There is no evidence showing how many confirmatory tests should be

performed to maximize PA's diagnostic sensitivity, specificity, and cost-effectiveness (C).
Point 3. There is no evidence showing the superiority of any confirmatory test over the others. CCT, however, ought to be considered as the first option evaluating its safety and feasibility. We suggest choosing the optimal confirmatory tests considering each patient's clinical situation (2C).
CCT, captopril challenge test

Evidence and comments

Although the ARR is effective for PA screening and has a 64–94% sensitivity, previous reports suggest that 30–50% of subjects with positive screening results do not have PA [55]. Thus, it is essential to perform the confirmatory test of autonomous aldosterone hypersecretion. The guideline of the Endocrine Society recommends four confirmatory tests: the CCT, SIT, oral salt loading test (OSLT), and fludrocortisone suppression test [4]. However, the guidelines of the Japan Endocrine Society recommend the CCT, SIT, OSLT, and furosemide upright test (FUT) [6, 7].

A definitive clinical diagnosis of PA previously required at least two positive confirmatory tests, but currently only one positive test [4, 6, 7]. While increasing the number of positive tests may improve the diagnostic specificity for PA, no study has demonstrated how many confirmatory tests are optimal to maximize the diagnostic sensitivity and specificity for PA and the cost-effectiveness. One study showed that patients with two positive results in the confirmatory tests are associated with higher cardiovascular events than those with one positive result [56]. On the other hand, we cannot exclude PA when only one confirmatory test is negative. The additional tests should be decided on individual patients as needed.

A recent meta-analysis revealed similar PA diagnostic accuracies between CCT and SIT [57]. A comparative study in Chinese patients with hypertension showed that the CCT and SIT's diagnostic accuracy was comparable with the fludrocortisone suppression test [58]. Another head-to-head trial compared the ability of the CCT *versus* SIT to detect APA in patients with different sodium intake levels. The positive likelihood ratio of the SIT for diagnosing APA surpassed that of the CCT in patients with a sodium intake lower than 7.6 g/day. However, this difference was smaller at a higher sodium intake [59]. Therefore, there is no definitive evidence showing which confirmatory test is superior to the others under daily clinical practice [60].

Table 5 shows the characteristics of each confirmatory test. CCT is generally safe and easier to perform, even in outpatient clinics. This test may also be feasible for patients with heart failure who cannot undergo other tests. We need caution for angioedema, a rare but serious adverse effect of ACE. This guideline designated ARR ≥200 (PAC/PRA) or ≥40 (PAC/ARC) as a positive CCT result following the ARR in the screening. In addition, we set an ARR ranging from 100 to 200 (PAC/PRA) or from 20 to 40 (PAC/ARC) as the borderline and designated as provisionally positive (see CQ 5). We recommend individualized management for subtype testing and treatment considering each patient's desire and clinical findings (hypokalemia, an adrenal tumor on CT, *etc*.) (see CQ 22). Although PAC (>120 pg/mL by RIA) was used as an alternative criterion for a positive CCT [6],

Table 5 Comparison of the confirmatory tests for autonomous aldosterone hypersecretion

Test	Adverse effects and other remarks	Sensitivity*[1]	Specificity*[2]
Captopril challenge test	• Angioedema (rare)	70–100%	68–95%
Saline infusion test	• Increased blood pressure • Hypokalemia • Contraindicated for uncontrolled hypertension, renal failure, heart failure, profound hypokalemia, and severe cardiac arrhythmia	66–92%	72–97%
Furosemide upright test	• Hypotension • hypokalemia	Not determined	Not determined
Oral salt loading test	• Increased blood pressure • Hypokalemia • Contraindicated for uncontrolled hypertension, renal failure, heart failure, profound hypokalemia, and severe cardiac arrhythmia • Concern over the creditability of urine collection • High false-positive rate in case of renal failure	96%? (Insufficient evidence)	93%? (Insufficient evidence)

*1, *2 Data from various reports

the rate of positive results was lower than with the ARR criterion [61], and its diagnostic significance needs further investigation.

SIT is also widely used as a confirmatory test. A very recent study has demonstrated that a post-SIT PAC (measured by CLEIA) of 61.6 pg/mL had a sensitivity and specificity for diagnosing PA of 95.4% and 80.0%, respectively, and that a PAC of 78.2 pg/mL had a sensitivity and specificity of 86.7% and 86.2%, respectively [49]. The authors concluded that PA is highly likely if the PAC is >78.2 pg/mL, and PA can be excluded if the PAC is <61.6 pg/mL. The PAC between 61.6–78.2 pg/mL was set as the gray zone. In line with these data by CLEIA [49], we decided PAC of 60 pg/mL by CLEIA as the cut-off for SIT in the revised guideline. However, a PAC of 60 pg/mL by RIA, the cut-off for SIT in Japan, corresponds to a concentration of 12.2–15.1 pg/mL by CLEIA [37, 39]. Therefore, a PAC between 12 to 60 pg/mL was set as the borderline range and designated to be provisionally positive until the optimal cut-off of PAC by CLEIA is established. For those patients who showed PAC in the borderline range, the subsequent medical management for subtype diagnosis with AVS and treatment should be individualized as in CCT (see CQ 22). Although some studies have reported that seated SIT is superior to recumbent SIT in reducing the false-negative rate [62], the difference between the two positions remains unknown in Japanese patients with PA. Because SIT may induce hypokalemia and increase blood pressure, we should not indicate patients with uncontrolled hypertension, renal failure, heart failure, profound hypokalemia, and severe cardiac arrhythmia.

FUT has long been one of the confirmatory tests in Japan. Since FUT may cause collapse or unconsciousness due to hypotension or hypokalemia, we should strictly indicate and carefully observe the patients during the test. Although OSLT shows high diagnostic accuracy, low reproducibility [63], risks in patients with severe hypertension or cardiac dysfunction, and false-negative results in renal impairment limit its wider implementation.

Table 6 shows the comparison of previous and new diagnostic criteria for the confirmatory tests and screening of PA. Based on its safety and feasibility, CCT would be the first line confirmatory test for PA followed by SIT. However, careful consideration of the comorbidities and the medical environment for conducting the tests is required to choose the optimal test in an individual patient.

CQ 7. Which cases do not require confirmatory test?

Point 1. We suggest confirming the diagnosis of PA by bypassing confirmatory tests with spontaneous hypokale-

Table 6 Comparison of the previous and new diagnostic criteria for PA screening and confirmatory tests

	Previous criteria for positive results	New criteria for positive results
Screening test	PAC*1/PRA (ARR) >200 and PAC*1 >120 pg/mL	1-1 ARR (PAC*2/PRA) ≥200 and PAC*2 ≥60 pg/mL 1-2 ARR (PAC*2/PRA) 100–200*3 and PAC*2 ≥60 pg/mL 2-1 ARR (PAC*2/ARC) ≥40 and PAC*2 ≥60 pg/mL 2-2 ARR (PAC*2/ARC) 20–40*3 and PAC*2 ≥60 pg/mL
Captopril challenge test	After 60 min/90 min, 1. ARR (PAC*1/ PRA) >200 2. ARR (PAC*1/ ARC) >40 3. PAC*1>120 pg/mL	After 60 min/90 min, 1-1. ARR (PAC*2/PRA) ≥200 1-2. ARR (PAC*2/PRA) 100–200*3 2-1. ARR (PAC*2/ARC) ≥40 2-2. ARR (PAC*2/ARC) 20–40*3
Saline infusion test	After 4 h, PAC*1 >60 pg/mL	After 4 h, 1-1. PAC*2 ≥60 pg/mL 1-2. PAC* 2 12–60 pg/mL*3
Furosemide-upright test	After 2 h, 1. PRA <2.0 ng/mL/h 2. ARC <8.0 pg/mL	After 2 h, 1. PRA <2.0 ng/mL/h 2. ARC <8.0 pg/mL
Oral salt loading test	Urinary aldosterone concentration*1 >8 μg/day (Urinary sodium level >170 mEq/day)	Urinary aldosterone concentration >6 μg/day*4 (Urinary sodium level >170 mEq/day)

*1 PAC as measured by RIA.
*2 PAC as measured by CLEIA.
*3 Given the dissociation of the PAC values by RIA and CLEIA, borderline ranges were set for the ARR of the screening and CCT and the PAC of the SIT, and provisionally designated as positive for screening and confirmatory tests (see CQ 5, CQ 6).
*4 Reference value generated by the conversion formula of PAC from RIA to CLEIA when the daily urine volume is 1.5 L. No evidence has been established with PAC by CLEIA.

mia (serum potassium concentrations <3.5 mEq/L), high baseline PAC (>100 pg/mL*[1]), and renin suppression in cases with a positive PA screening test. (2B).
*1 Measured by CLEIA

Evidence and comments

In principle, we recommend confirmatory tests to confirm aldosterone hypersecretion in cases with a positive screening result. According to the 2019 guideline of the Japanese Society of Hypertension (JSH), we can bypass the confirmatory test in patients with an ARR >1,000 and PAC >200 pg/mL (by RIA) [7]. According to the Endocrine Society clinical practice guideline for PA, we can bypass the confirmatory test in cases with spontaneous hypokalemia, a PAC >200 pg/mL, and renin suppression [4]. According to the French Endocrine Society guideline, we can confirm PA diagnosis in cases with positive screening results (ARR >300 and baseline PAC >90 pg/mL) or a baseline PAC >200 pg/mL at two different opportunities [64, 65].

In the JPAS, involving 2,340 PA patients, a baseline PAC >308.5 pg/mL on RIA (>171 pg/mL on CLEIA) and PRA <0.6 ng/mL/h were considered criteria for bypassing confirmatory test [66]. In another Japanese study involving 252 PA and 75 non-PA patients, a PAC >300 pg/mL on RIA (>166 pg/mL on CLEIA), or a PAC of 200–300 pg/mL on RIA (100–166 pg/mL on CLEIA) plus hypokalemia, was an indication for bypassing confirmatory test [67]. In a Chinese report involving 518 PA and 266 non-PA patients, a PAC >200 pg/mL, ARC <2.5 μIU/mL (PRA <0.4 ng/mL/h), and hypokalemia were indications that confirmatory test can be bypassed [68]. Below the detection limit of renin varies depending on the measurement method used, but PRA <0.5 ng /mL/hr and ARC <2.5 pg/mL are generally used as a cut-off for judgment.

CQ 8. What are the indications for dexamethasone suppression testing?

Point 1. We recommend conducting the dexamethasone (1 mg) suppression test for patients with adrenal tumors detected by computed tomography (CT) to evaluate the presence of cortisol co-secretion (2C).

Evidence and comments

The prevalence of adenomas with aldosterone and cortisol co-secretion is 3.9–77.6% in PA [69] and 23.4% in unilateral PA [25]. In addition, pathological findings from adrenalectomy for APA have demonstrated expression of the enzymes associated with cortisol production in most cases (CYP17A1: *n* = 21/21, 100%; CYP11B1: *n* = 17/21, 81%) [70]. Aldosterone and cortisol co-secreting adenomas have several clinical characteristics, including larger size (>20 mm) and higher rates of glucose intolerance, osteoporosis, proteinuria, and cardiovascular events compared with aldosterone-producing adenomas [21, 25, 71-74]. In addition, cortisol co-secretion in APA suppresses contralateral adrenal cortisol secretion, affecting the interpretation of AVS results and the need for postoperative steroid treatment. Thus, it is clinically important to evaluate the presence of cortisol co-secretion in APA. We recommend the dexamethasone (1 mg) suppression test for patients with adrenal tumors detected by CT. An expert consensus statement [75] also recommended the dexamethasone suppression test before AVS in patients with APA >3.0 cm in diameter to evaluate autonomous cortisol co-secretion. In cases of autonomous cortisol co-secretion in APA, the ipsilateral side is not always responsible for the co-secretion [71], and the AVS result should be evaluated carefully (see CQ 10, CQ 21).

Thus, we recommend the dexamethasone (1 mg) suppression test for patients with adrenal tumors detected by CT, considering the high prevalence of aldosterone and cortisol co-secreting adenomas. A cut-off plasma cortisol level of ≥1.8 μg/dL by the dexamethasone suppression test is recommended for diagnosing autonomous cortisol co-secretion [76].

Subtype testing

CQ 9. What is the purpose of PA subtype testing?

Point 1. Adrenalectomy of the affected side of PA is highly effective for normalizing the PAC, cure/ improvement of hypertension, and improvement/prevention of target organ damage. The subtype testing aims to diagnose the unilateral subtype of PA (1A).

Evidence and comments

Adrenalectomy of the affected side is the optimal treatment to normalize aldosterone excess, cure hypertension, and reduce the dose of antihypertensive medicines in patients with unilateral PA. As a treatment for unilateral lesions, adrenalectomy is superior to MRAs in terms of biochemical and clinical outcomes, prevention of organ damage progression, and prognosis [77, 78] (see CQ 17, CQ 23). The purpose of subtype testing is to diagnose unilateral PA.

CQ 10. What is the most appropriate modality for PA subtyping?

Point 1. We recommend AVS as the optimal method for functional subtyping PA when surgical treatment is feasible and desired by the patient (1A).

Point 2. Although prediction models incorporating patient background characteristics, clinical data, and imaging findings contribute to the subtype diagnosis of

PA (2C), we recommend AVS for precise diagnosis of the PA subtype before adrenalectomy.

Evidence and comments

The concordance rate between AVS and adrenal imaging such as CT and magnetic resonance imaging (MRI) in diagnosing the PA subtype is 38–81% [79-81]. A systematic review showed that the PA subtype was a misdiagnosis of the PA subtype was experienced in 37.8% of the cases [82]. Therefore, AVS with a sensitivity of 95% and a specificity of 100% is more valuable than CT or MRI [4]. The JPAS showed that the concordance rate of AVS and CT among 1,591 PA patients was 45.4% (297/654) for unilateral PA diagnosis and 85.4% (768/899) for bilateral PA diagnosis [80]. Another study evaluating the effect of age on PA subtyping among 358 patients with hypokalemia reported diagnostic concordance rates of 90% (27/30) in patients aged <30 years, 79% (31/39) in those aged 35–39 years, and 69% (198/289) in those aged ≥40 years; the concordance rate between AVS and CT based on the surgical outcome was 100% (30/30) in patients aged <35 years and 87% (34/39) in those aged 35–40 years [83]. Moreover, the biochemical cure rate is higher after surgery in patients diagnosed with AVS than CT [84]. Altogether, we recommend AVS for patients undergoing unilateral adrenalectomy. However, we suggest bypassing AVS in patients aged <35 years with spontaneous hypokalemia, marked aldosterone excess, or a unilateral adrenal lesion with radiological features consistent with cortical adenoma on CT, and patients may proceed directly to unilateral adrenalectomy (see CQ 12).

Based on clinical findings, various prediction models of the PA subtype have been reported for use instead of AVS. In the JPAS, PA patients (n = 1,936) were divided into to the development group (n = 1,290) and the validation group (n = 646). A prediction scoring model was developed based on the following parameters: serum potassium concentrations (>3.9 mEq/L, 4 points; 3.5–3.9 mEq/L, 3 points), no adrenal mass on CT (3 points), baseline PAC (RIA) <210.0 pg/mL (2 points), baseline ARR (RIA) <620 (2 points), and female sex (1 point). A score ≥8 points had an accuracy for diagnosing bilateral PA of 93.5% [85]. Another model showed that female sex, ARR ≤550, and potassium concentrations ≥3.8 mM were independent predictors of bilateral PA in 393 PA patients without an adrenal mass on CT, and receiver operating characteristic analysis revealed 29% sensitivity and 96% specificity for diagnosing bilateral PA when all three parameters were fulfilled [79]. The concordance rate of AVS and CT in patients with a unilateral mass on CT was 70.6% (266/377) in patients with hypokalemia and 23.8% (66/277) in patients with normokalemia. In contrast, the respective rates in patients with normal adrenal CT findings were 38.1% (90/236) *versus* 6.2% (41/663) [80]. These prediction models help predict the subtype and determine AVS indications. However, in the absence of evidence for a comparative diagnostic accuracy with that of AVS, no prediction model cannot presently replace AVS, and we recommend AVS for accurate subtyping of PA.

The essential aim of AVS is determining the PA subtype, especially unilateral PA, in cases eligible for surgical treatment. It is, therefore, crucial to use the AVS results efficiently in treatment decision-making because of the invasive nature and high cost of AVS. Recently, a retrospective, multinational, multicenter, comparative study of AVS (AVSTAT) showed that one-fourth of the patients diagnosed with unilateral PA did not receive surgical treatment because of various clinical reasons [17]. We recommend AVS only when the indication is strong and after obtaining adequate informed consent and careful evaluation of the clinical data.

CQ 11. What are the characteristics and standard implementation policies of imaging study?

Point 1. CT is easier and less costly to perform in Japan, while there is no apparent difference in sensitivity or specificity between CT and MRI in detecting adrenal adenomas. We, therefore, recommend CT for the initial imaging study of PA (1B).

Point 2. We recommend contrast-enhanced dynamic MDCT when implementing AVS because MDCT has a high spatial resolution and can reduce the burden on patients by shortening the imaging time and confirming the adrenal veins (2C).

Point 3. There is a high risk of developing contrast-induced nephropathy in patients with CKD stage G4 or higher. We recommend intravenous saline infusion prior to CT with sufficient informed consent if the need to use contrast media is high and the benefits outweigh the risks (1A).

Point 4. We suggest adrenocortical scintigraphy/single-photon emission CT (SPECT) with dexamethasone as an additional modality in patients with typical PA findings (*e.g.*, hypokalemia and adrenal tumors on CT) when AVS is difficult to perform or unsuccessful, or the patient refuses AVS (2C).

MDCT, multidetector-row computed tomography; CKD, chronic kidney disease

Evidence and comments

Subtype testing, unilateral or bilateral, is required in patients with a positive PA confirmatory test and a desire to undergo surgery. The Endocrine Society clinical practice guideline [4] recommends CT for the subtype

diagnosis, excluding adrenal cancer, and obtaining the exact anatomical information for interventional radiologists and surgeons. The guideline of the Japan Endocrine Society [6] also states that abdominal CT is essential for the differential diagnosis of various adrenal tumors. Comparing CT and MRI for subtype testing, CT had a sensitivity of 85%, specificity of 95%, positive predictive value (PPV) of 95%, and negative predictive value of 86.5%, and the respective values of MRI were 85%, 95%, 89.5%, and 86.5%, with no difference between CT and MRI except for a higher PPV with CT [86]. Therefore, CT is recommended as the first-line imaging modality in Japan because of the shorter examination time and lower cost compared with MRI. Since most APA are small tumors, we recommend thin-slice CT. However, because the incidence of nonfunctional adenomas in the adrenal glands is high, and CT cannot detect some aldosterone-producing microadenomas, the sensitivity and specificity of CT for subtype testing of PA are not sufficient for a precise subtype diagnosis. Therefore, we recommend AVS for subtype testing [81, 87]. We recommend MRI for children and pregnant women because of concerns about radiation exposure, but MRI should not be performed at less than four months of gestation to protect the fetus.

MDCT can shorten the imaging time and reduce the burden on patients by obtaining numerous tomographic images at a time. It is superior to single-detector row CT in terms of sensitivity and specificity by creating 3D images *via* a high spatial resolution. In addition, contrast-enhanced dynamic MDCT can detect the right adrenal vein, which helps improve the success rate of AVS [88, 89].

We recommend monitoring CIN when using contrast medium in CKD patients. The 2018 CKD clinical practice guideline [90] states that the risk of developing CIN is high at CKD stage G3a or higher (eGFR <60 mL/min/1.73 m^2) and even higher when the eGFR is less than 45 mL/min/1.73 m^2 or the dose of contrast medium is high. On the other hand, according to the 2018 guideline on the use of iodinated contrast medium in patients with kidney disease [91] and the 2020 American College of Radiology Manual on contrast medium [92], intravenous administration of contrast medium confers a lower risk of CIN than previously thought. The risk of developing CIN is low if the eGFR is higher than 30 mL/min/1.73 m^2. However, even at this eGFR, the risk factors for CIN (*e.g.*, older age, diabetes, eGFR <60 mL/min/1.73 m^2) should be evaluated, and we recommend taking appropriate preventive measures. We recommend intravenous saline infusion and sodium bicarbonate to prevent CIN in patients at high risk of developing CIN [92-94]. We do not recommend drinking water due to insufficient evidence of its efficacy [90-92]. In patients at high risk of developing acute adverse effects, such as allergic reactions to iodine contrast medium and gadolinium contrast medium, premedication with steroids and antihistamines should be considered to reduce the risk of such adverse effects after obtaining sufficient informed consent [92, 93]. Gadolinium contrast medium is reportedly helpful for AVS in patients with an allergy to iodine contrast medium, but it is not covered by medical insurance in Japan [94].

Adrenocortical scintigraphy for PA (131I-6-beta-iodomethyl-19-norcholesterol [NP-59]) is performed under dexamethasone suppression. Compared with conventional planner images, NP-59 SPECT/CT improves both the sensitivity and PPV of subtype testing (sensitivity, 40.9% *vs.* 81.8%; specificity, 66.7% *vs.* 66.7%; PPV, 75.0% *vs.* 85.7%) [95, 96]. Therefore, dexamethasone-suppressed adrenocortical scintigraphy is an alternative to AVS in patients with a desire and indication for surgery but who cannot undergo AVS due to iodine allergy or other reasons, in patients who do not wish to undergo AVS, or in patients with inconclusive AVS results. However, in a quantification study of planner images, NP-59 accumulation was strongly correlated with the tumor volume and weakly correlated with the ability to secrete aldosterone [97]. In addition, there are disadvantages, such as a limited number of medical facilities that perform this test and concern about inducing hyperglycemia in cases with impaired glucose tolerance. NP-59 is not available in the United States.

CQ 12. In what cases can AVS be bypassed and treatment selected?

Point 1. We suggest considering unilateral adrenalectomy by bypassing AVS after obtaining enough informed consent in patients younger than 35 with typical clinical findings of PA (hypokalemia, a unilateral adrenal tumor on CT, high PAC) who are more likely to have unilateral disease (2B).

Point 2. Patients with normokalemia and no adrenal tumors on CT are more likely to have bilateral disease, in which case we suggest drug therapy taking into consideration other clinical features (sex, age, body mass index [BMI], PAC, ARR, and results of confirmatory test) and by bypassing AVS after obtaining enough informed consent (2B).

Evidence and comments

We recommend AVS as the optimal method for subtype diagnosis of PA prior to adrenalectomy. However, given its invasive nature, AVS avoidance should always be considered if applicable, especially in patients with a very high probability of unilateral or bilateral disease based on clinical findings. According to the Endocrine

Society clinical practice guideline, patients with all the following conditions can proceed directly to unilateral adrenalectomy without AVS: aged <35 years, hypokalemia (<3.5 mEq/L), a high PAC (>300 pg/mL), and unilateral adrenal tumors on CT [4]. The JPAS demonstrated favorable outcomes after unilateral adrenalectomy of the tumor side in patients younger than 35 years of age with hypokalemia (<3.5 mEq/L), a high PAC (above the upper limit of normal), and a unilateral adrenal tumor (>1 cm) on CT [83]. AVS could be bypassed in patients meeting each of these criteria after obtaining adequate informed consent. In patients older than 35 years of age, we recommend AVS because the rate of nonfunctioning adenomas increases with age.

In the JPAS, the rate of unilateral PA was as low as 6.2% in patients with no adrenal tumors on CT and normal serum potassium concentrations (>3.5 mEq/L), indicating that AVS is weakly recommended [80]. In addition to this, a mildly elevated basal PAC (<210 pg/mL) [85], mildly elevated ARR (<550) [79], obesity (BMI >25 [98, 99], especially in male patients younger than 40 years of age [100]), and female sex [79] (especially when older than 60 years of age [100]) were predictive of bilateral PA. The absence of adrenal tumors on CT and normokalemia have been the most important predictors of bilateral PA [79, 85, 98].

A more recent study demonstrated that many patients with unilateral PA had been treated with antihypertensive drugs based on various clinical findings that were apparent even before AVS [17]. Therefore, we should not uniformly indicate AVS in patients with subtypes very likely to be unilateral or bilateral, reasonable blood pressure control, normokalemia, or various comorbidities. It is crucial to strictly indicate AVS considering the desires and conditions of each patient after obtaining adequate informed consent on the benefits and disadvantages of the procedure.

Adrenal venous sampling (AVS)

CQ 13. What methods can improve the success rate of AVS?

Point 1. We recommend performing AVS by standardized protocols at specialized medical centers by experienced radiologists (1A).

Point 2. To improve the success rate of AVS, we recommend obtaining anatomical information of the adrenal vein by preoperative MDCT, intraoperative use of ACTH, confirmation of the catheter position by intraoperative imaging and rapid intraoperative cortisol measurements (1C).

ACTH, adrenocorticotropic hormone; MDCT, multidetector-row computed tomography

Evidence and comments

AVS requires technical proficiency. We suggest various ingenuities [6] and standardized protocols at specialized medical centers with experienced radiologists [101, 102] to improve its success rate. If without ACTH stimulation, we recommend performing in the morning. Rest and sedatives, if necessary, are recommended before AVS to minimize the effects of stress. Blood samples should be obtained at least 15 min after the start of AVS [75]. There are two methods for inserting catheters into the adrenal veins: a sequential method in which catheter insertion into the adrenal vein proceeds from right to left in sequence and a simultaneous method in which blood samples are collected simultaneously from the left and right adrenal veins using two catheters. We recommend deciding the detailed protocol to facilitate the procedure and improve the AVS success rate. No report has examined the difference in success rate between the sequential and simultaneous methods.

Preoperative identification of the adrenal vein by MDCT improves the success rate [88, 103-108]. ACTH stimulation during AVS facilitates judging the success of catheterization and improving the success rate [75, 109, 110], but the method of ACTH administration must also be determined in advance (see CQ 14). Contrast radiography during AVS helps determine the proper catheter position in the adrenal vein, but it is essential to inject the contrast medium slowly to avoid rupture of the adrenal vein [102]. Rapid intraoperative cortisol measurements improve the AVS success rate by confirming the proper catheter positioning [88, 98, 111]. Table 7 summarizes the measures to improve the success rate of AVS.

Table 7 Summary of the measures to improve the success rate of adrenal venous sampling

1. Implementation of AVS at experienced specialized medical centers.
2. Preoperative identification of the adrenal vein anatomy by MDCT.
3. ACTH stimulation to facilitate judgment of successful catheter insertion and to increase success rate.
4. Confirmation of the catheter position in the adrenal vein using contrast radiography.
5. Rapid intraoperative cortisol measurements.

CQ 14. Is ACTH stimulation recommended during AVS?

Point 1. ACTH stimulation increases the SI and improves the success rate of bilateral selective catheterization. We recommend ACTH stimulation during AVS (1B).

Point 2. There is no clear evidence that ACTH stimulation improves the diagnostic accuracy of laterality for AVS (C).

SI, selectivity index

Evidence and comments

Synthetic ACTH (Cosyntropin®) is administered during AVS to minimize stress-induced fluctuations in aldosterone secretion, maximize the cortisol gradient from the adrenal vein to the inferior vena cava, and maximize aldosterone secretion from APA. For these reasons, ACTH stimulation improves the success rate of bilateral selective catheterization and is common in over half of the major centers in the world [112]. We recommend using the selectivity index (SI), defined as the ratio of the cortisol levels in the adrenal vein to that in the inferior vena cava, to verify selective catheterization into the adrenal vein (see CQ 15). Although the success rate is significantly affected by the cut-off of SI, ACTH stimulation improved the success rate at any SI cut-off value, and we recommend therefore recommend to use in AVS [110].

Comparison of the PA subtype in the same patients demonstrated that ACTH stimulation increases the bilateral PA compared to without ACTH stimulation [113]. Effects of ACTH stimulation on the diagnostic accuracy of laterality vary from study to study: some studies demonstrated it better with ACTH stimulation [114, 115], and another study showed the opposite result [116]. The JPAS demonstrated that patients diagnosed as unilateral PA without ACTH stimulation and bilateral PA with ACTH stimulation had poor clinical and biochemical outcomes and a low incidence of adrenal adenomas as pathological findings, compared with those diagnosed as unilateral PA with and without ACTH stimulation. However, patients with lateralization index (LI) (see CQ 16) >8.3 without ACTH stimulation showed good surgical outcomes even with the bilateral diagnosis with ACTH stimulation. The results suggest that the laterality without ACTH stimulation is also helpful for the subtype diagnosis when the LI is high [113].

There are three different protocols for ACTH administration: IV bolus [114, 117], infusion [118], and IV bolus followed by infusion [115, 116]. If operators have enough experience with performing AVS, they can use an IV bolus; otherwise, either infusion or IV bolus followed by infusion can be used [75]. A high dose (250 μg) for IV bolus or 50–80 μg/h (250 μg total) for infusion is recommended [116]. The time interval between ACTH stimulation and blood sampling should be 15–30 min [114, 116-118], and we suggest an additional infusion of ACTH if the time interval exceeds 45–60 min. There is no clear evidence regarding which protocol is superior to others.

CQ 15. Which criteria do we recommend to evaluate successful catheterization in AVS?

Point 1. We recommend an SI ≥2 without ACTH stimulation and SI ≥5 with ACTH stimulation to confirm successful catheterization (1C).

SI, selectivity index

Evidence and comments

Successful catheterization in AVS is generally determined using the SI. The cut-off SI ranges from 1.1 to 3.0 without ACTH stimulation and from 2.0 to 5.0 with ACTH stimulation [82]. In a multicentric study of endocrine hypertension conducted at many referral centers worldwide, the cut-off SI was generally 2.0 without ACTH stimulation and 3.0 or 5.0 with ACTH stimulation [112]. A cut-off SI with ACTH stimulation of 5.0 was the criteria to show the most accurate laterality diagnosis [119]. In addition, an analysis comparing SI fluctuations without and with ACTH stimulation in the same patient showed that an SI of 1.4 without ACTH stimulation is equivalent to an SI of 5.0 with ACTH stimulation [120]. We recommend SI cut-offs of 2.0 and 5.0 without and with ACTH stimulation, respectively, are recommended in this guideline because they are strict and widely used.

Even if bilateral catheterization is successful using SI, determining the correct lateralization may be difficult in cases in which the ratio of aldosterone to cortisol levels (A/C) is lower in the adrenal vein than in the inferior vena cava on both sides, *i.e.*, apparent bilateral aldosterone suppression [121]. Possible causes include blood sampling during the quiescent period when aldosterone in the adrenal vein becomes low due to fluctuation of endogenous ACTH, dilution in the adrenal vein, and the presence of a drainage vein from an APA other than the adrenal vein. The prevalence of this phenomenon decreased with ACTH stimulation. In addition, it may be necessary to consider repeating AVS, segmental AVS, or blood sampling from a drainage vein other than the adrenal vein.

If catheterization of the adrenal vein is unsuccessful on one side, the A/C ratio between the successful side of the adrenal vein and inferior vena cava may be useful to predict the laterality: ipsilateral dominant if ≥5.5 and contralateral dominant if ≤0.5, respectively) [122, 123]. Suppose catheterization of the right adrenal vein is

unsuccessful, the combination of the ratio of A/C between the left adrenal vein and inferior vena cava and the A/C of the left adrenal vein may be useful to predict the laterality: left dominant if ≥1 and >68, right dominant if <1 and <9, respectively [124]. Since the reliability of these methods is limited, we suggest repeating AVS.

In cases with suppressed cortisol levels in the contralateral adrenal vein due to cortisol co-secretion from the adenoma, catheterization may be judged as successful if PAC in the contralateral adrenal vein is significantly higher (7.2–510.5 fold [125], 77.5-fold [126]) than that in the inferior vena cava or peripheral vein,

CQ 16. Which criteria do we recommend to distinguish between unilateral and bilateral PA in AVS?

Point 1. We recommend an ACTH-stimulated LI >4 as an indication of unilateral PA for adrenalectomy (1B). Some reports have demonstrated that the ACTH-stimulated CR <1 is a criterion for distinguishing between unilateral and bilateral PA. We suggest a combination of the LI and CR for cases requiring strict indications for unilateral adrenalectomy (2B).

Point 2. In cases with a borderline ACTH-stimulated LI (2–4) or discrepant lateralization between the different criteria or with and without ACTH stimulation, we recommend a comprehensive diagnosis of laterality considering a CR <1, the PAC in the adrenal vein, and clinical manifestations (*e.g.*, hypokalemia, adrenal CT findings, age) (1B).

Point 3. Since the LI could be interfered with by the autonomous cortisol co-secretion, we recommend determining the laterality comprehensively by taking into consideration the PAC in the adrenal vein and its left-right ratio as well as the LI (1C).

CR, contralateral ratio; LI, lateralization index

Evidence and comments

Of the various criteria for distinguishing unilateral from bilateral PA, the LI defined as the ratio of the aldosterone to cortisol levels in the dominant adrenal vein divided by that in the non-dominant adrenal vein with the cut-off values >4 with ACTH stimulation has been recommended for the indications of unilateral diagnosis and adrenalectomy [4, 6]. An ACTH-stimulated LI >4 is an independent predictor of a biochemical cure and postoperative outcome six months after unilateral adrenalectomy [127]. The PASO study also accepted the criteria to verify the prognosis of unilateral PA after adrenalectomy [128]. Although contralateral ration (CR), defined as the ratio of the aldosterone to cortisol levels in the non-dominant adrenal vein divided by that in the inferior vena cava or peripheral vein, as a predictor of the clinical outcome after unilateral PA has yet unestablished [129], we suggest using a CR <1 in combination with an ACTH-stimulated LI >4 for a strict indication of unilateral adrenalectomy.

Although an ACTH-stimulated LI >2.6–3 has been reported to indicate unilateral PA [4, 5], the LI in this range overlaps with EH [130]. Therefore, we recommend a comprehensive diagnosis of the subtype to improve the diagnostic accuracy by combining the LI and other findings such as a CR <1 [6], the PAC in the adrenal vein, and clinical manifestations (*e.g.*, low serum potassium concentrations [<3.5 mEq/L], a unilateral adrenal tumor on CT, aged <35 years, female sex, and ARR >550) as predictors of unilateral PA [79, 80, 83]. The odds ratio of unilateral PA patients with unilateral adrenal tumors >10 mm on CT and hypokalemia was 36.4 compared with patients with normal bilateral adrenal glands on CT and normokalemia.

Co-secretion of cortisol from the adenoma decreases the SI on the contralateral side and affects the evaluation of successful catheterization in AVS. In addition, it decreases the A/C of the dominant side and increases that of the non-dominant side, leading to a decrease in the LI and a false-negative result of unilateral PA [6, 125]. We, therefore, recommend determining the subtype diagnosis comprehensively by considering not only the LI but also the PAC in the adrenal vein and its ratio between the right and left adrenal.

Therefore, patients with apparent adrenal tumors on CT should undergo the dexamethasone (1 mg) suppression test before AVS (see CQ 8). The lesion sites for autonomous secretion of aldosterone and cortisol do not always ipsilateral.

Treatment and prognosis

CQ 17. What is the treatment policy for PA?

Point 1. We recommend adrenalectomy on the affected side in patients with unilateral PA because it can cure the disease, normalize aldosterone excess and hypertension, and improve or prevent the progression of target organ damage (1A).

Point 2. We recommend medical treatment with MRAs in patients with bilateral PA or unilateral PA with no indication for or no patient desire for surgery (1A).

Point 3. We recommend normalization of blood pressure and serum potassium concentrations and release of renin suppression as the treatment goals with MRAs and careful monitoring of serum potassium concentrations and target organ damage, including renal function. (1B).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

In patients with unilateral PA, adrenalectomy of the lesion side improves hypertension and hypokalemia

associated with aldosterone excess [4, 7, 77, 128]. A multicenter international study has demonstrated that the biochemical cure rate was 94% after adrenalectomy [128]. Although there are no established criteria for when to judge biochemical cure after adrenalectomy, PAC usually shows a significant decrease in the early period after surgery (about one week). It usually becomes below the measurement sensitivity if by the CLEIA method. It takes more than a month to suppression of renin and the aldosterone secretion from the contralateral adrenal gland to recover. However, the recovery period depends on the severity and duration of aldosterone excess. In contrast, the cure rate for hypertension (clinical cure) is only about 30–52% [4, 131] and 18% in the elderly [127]. Various lifestyles predisposing to hypertension [4, 128] and concurrent disorders such as obstructive sleep apnea syndrome, renal dysfunction, and obesity [28, 127, 132] attribute to residual hypertension. It remains unclear whether surgery has a prognostic advantage over medical therapy beyond reducing the number of medications [4, 6, 7, 133]. However, adrenalectomy was more effective than medical treatment in terms of new incidence of end-stage renal disease and overall survival rates [78, 134-136]. We, therefore, recommend adrenalectomy as the preferred treatment for unilateral PA [4, 6, 7]. Laparoscopic adrenalectomy is the first choice of surgery, and appropriate preoperative management of hypertension and hypokalemia with MRAs is mandatory [4, 6, 7]. (see CQ 18)

In patients with bilateral PA or unilateral PA not indicated to surgery due to complications or patient preference, medical treatment with MRAs is the first-line therapy [6, 7]. Table 8 provides an overview of the three MRAs approved by medical insurance in Japan. The beneficial effects of MRAs on overall survival depend on the dose [78, 135]. We recommend achieving the treatment goals, normalization of blood pressure and serum potassium concentrations, and the release of renin suppression (PRA ≥one ng/mL/h), using a sufficient dose of MRAs [134-137]. However, hyperkalemia [4, 6, 7, 138]

Table 8 MRAs approved by medical insurance in Japan

Name	Spironolactone	Eplerenone	Esaxerenone
Formulation	25 mg tablet 50 mg tablet 10% granules	25 mg tablet 50 mg tablet 100 mg tablet	1.25 mg tablet 2.5 mg tablet 5 mg tablet
Indications	1. Hypertension (*e.g.*, essential, renal) 2. Cardiac edema (Congestive heart failure) 3. Renal edema 4. Hepatic edema 5. Idiopathic edema 6. Edema and ascites related to malignancy 7. Edema related to malnutrition 8. Diagnosis and management of PA	1. Hypertension 2. Chronic heart failure (Approved only for patients on basic medications including ACE inhibitors, ARBs, beta blockers, and diuretics)	Hypertension
Administration method	• Divided dose of 50–100 mg/day. • Commonly combined with other medicines excepting for diagnosis and management of PA.	• Hypertension: 50 mg/day (max. 100 mg/day) • Chronic heart failure: 25 mg/day (max50 mg/day). • Start with 25 mg every other day in patients with moderate renal impairment (max. 25 mg/ day).	• 2.5 mg/day (max. 5 mg/day) • Start 1.25 mg/day for diabetes mellitus with microproteinuria or proteinuria.
Contraindication	1. Anuria or chronic renal failure 2. Hyperkalemia 3. Addison's disease 4. Use of tacrolimus, eplerenone, or mitotane 5. Allergy to spironolactone	1. Allergy to eplerenone 2. Hyperkalemia 3. Severe renal impairment 4. Severe hepatic impairment 5. Use of potassium-sparing diuretics 6. Use of itraconazole, ritonavir, and nelfinavir (for hypertension) 7. Diabetes mellitus with microalbuminuria or proteinuria 8. Moderate to severe renal impairment 9. Use of potassium supplementation	1. Allergy to esaxerenone 2. Hyperkalemia 3. Severe renal impairment 4. Use of potassium-sparing diuretics 5. Use of other MRAs 6. Use of potassium supplementation

and a decrease in eGFR [4, 6, 7, 24, 135, 137] sometimes occur in the early stage after the administration of MRAs. We, therefore, recommend starting with a low dose of MRAs and carefully monitoring serum potassium concentrations and target organ damage, including renal function, to prevent adverse events (see CQ 18, CQ 24).

If hypertension is not controlled by MRAs alone, we recommend the addition of other antihypertensive medicines such as calcium channel blockers, which have little effect on the fluid volume and renal function [7]. In patients with refractory hypokalemia, we suggest combining the MRAs with potassium preparation. Although spironolactone (SPL) can be used with potassium preparations in Japan, gynecomastia in male patients prevents its continuation. Eplerenone (EPL) or esaxerenone (ESA), which has higher selectivity to MR, is contraindicated with potassium preparations (Table 8). We should carefully indicate the combination of EPL or ESA and potassium preparations based on the judgment of the therapeutic benefit outweighing the risk and after obtaining adequate informed consent from the patients.

CQ 18. What are the crucial points of perioperative management of PA?

Point 1. Since the prevalence of resistant hypertension, hypokalemia, and cardiovascular complications is higher in patients with unilateral PA than with bilateral PA and EH, we recommend appropriate treatment of the complications before adrenalectomy to reduce risks during general anesthesia and adrenalectomy (1B).

Point 2. We recommend MRAs as the first-line medication to control hypertension and hypokalemia before adrenalectomy (1B).

Point 3. Since hyperkalemia and decreased eGFR are frequently observed early after adrenalectomy, we recommend carefully monitoring and managing serum potassium concentrations and renal function (1B). Elderly, low eGFR and suppressed aldosterone secretion on the nondominant adrenal side are the risk factors for hyperkalemia after adrenalectomy (C).

Point 4. After adrenalectomy, we recommend glucocorticoid replacement therapy in patients with unilateral PA co-secreting cortisol (1B).

EH, essential hypertension; MRAs, mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate

Evidence and comments

Resistant hypertension, hypokalemia, and cardiovascular complications are common in patients with unilateral PA [11, 27]. Perioperative hypokalemia is at risk for atrial fibrillation [139]. Therefore, appropriate treatment of these complications before adrenalectomy is essential to reduce the risk associated with general anesthesia and surgery. Blood pressure target value for elective surgery under general anesthesia is less than 160/100 mmHg, and blood pressure control prioritizes over surgery above 180/110 mmHg [7]. We recommend MRAs as the first-line medication to control hypertension and hypokalemia before adrenalectomy [4]. If the control of blood pressure and hypokalemia is inadequate by MRAs alone, we recommend the addition of other antihypertensive medicines and potassium preparations, respectively (see CQ 17).

Hyperkalemia [127, 138, 140] and a decrease in eGFR [24, 127, 137] occur after adrenalectomy. The prevalence of hyperkalemia after adrenalectomy was 9.9% in Japan [138] and 3.3% (transient) and 7.7% (persistent) in Korea [140], respectively. It is necessary to monitor serum potassium concentrations and renal function and appropriate treatment after adrenalectomy (see CQ 24). Elderly [24, 127, 138, 140], longer history of hypertension [140], low eGFR [24, 138, 140], larger tumor size [140], and suppressed aldosterone secretion on the nondominant side of adrenal [141] are the risk factors for hyperkalemia. We recommend taking immediate measures such as restricting potassium intake, and optimizing salt intake and doses of antihypertensive drugs, including MRAs, to avoid excessive hypovolemia and hypotension at the early onset of postoperative hyperkalemia, especially in patients with these risk factors.

PA occasionally co-secretes cortisol [25, 69] (see CQ 8). Since 20% of the patients with PA co-secreting cortisol developed adrenal insufficiency [69], we recommend starting glucocorticoid replacement therapy during or after adrenalectomy. We should optimize the dose and duration of glucocorticoid replacement depending on the severity of autonomous cortisol co-secretion [142].

CQ 19. Is there any difference in the treatment effects among MRAs?

Point 1. There is no clear evidence to support differences in treatment effects among MRAs. Approved doses and precautions for the use of each MRA could affect drug selection (B).

Point 2. Which MRAs to use should be determined by considering antihypertensive effects, effects of improving hypertensive target organ damage, adverse effects, tolerability, gender, medical costs in addition to the precautions for use (1A).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

Three kinds of MRAs (SPL, EPL, and ESA) are available in Japan. The first randomized study demonstrated

that the antihypertensive effects of EPL (50 to 200 mg/day) and SPL (50 to 400 mg/day) were comparable in patients with bilateral PA [143]. Another randomized study demonstrated, however, that the decrease in systolic and diastolic blood pressure was more significant with SPL (75–225 mg/day) than with EPL (100 to 300 mg/day) in patients with PA (n = 141) [144]. In a prospective observational study, blood pressure and renal function were comparable, but serum potassium concentrations were lower, but the number of antihypertensive agents was higher with EPL than with SPL [145]. A randomized study in PA patients in Japan showed no significant difference in blood pressure, serum potassium concentrations, and renal function between treatment with EPL (25–100 mg/day) and SPL (12.5–100 mg/day) [146]. There is no evidence to show differences in the antihypertensive effects between SPL and EPL at the approved doses in Japan. No study has compared the effects of ESA with EPL or SPL. In addition, there is no evidence to support differences among MRAs in the effects on long-term prognosis and target organ damages in PA.

Gynecomastia in males and breast pain in females are more frequent with SPL than other MRAs due to its low selectivity to MR [10]. SPL was prescribed more frequently in female than male patients with bilateral PA [147]. However, the time-dependent decrease in eGFR associated with MRAs was more pronounced with SPL than EPL and in female patients than in male patients. SPL use was an independent predictor of a more significant eGFR decrease in female patients [147]. In addition, the precautions and contraindications for use vary between MRAs. It is contraindications to use a potassium preparation with EPL or ESA but not with SPL [7].

CQ 20. Is specific treatment with MRAs necessary even in patients with PA under reasonable blood pressure control and normal serum potassium concentrations by conventional antihypertensive medicines?

Point 1. We recommend MRAs for the treatment of PA to prevent target organ damage through a direct action of aldosterone, even in patients with reasonable blood pressure control and normokalemia by standard medication (1C).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

We should consider three factors in treating patients with PA under reasonable blood pressure control: direct effects of excess aldosterone on the target organ damage, possible masked hypertension despite good office blood pressure, and increased risk of future hypertension and cardiovascular events. Aldosterone excess directly causes various target organ damage in PA. PAC is an independent risk factor for cardiovascular events [11], renal dysfunction, and proteinuria [18]. The prevalence of cerebrocardiovascular disease was greater in patients with a higher PAC [20]. In addition, left ventricular hypertrophy was significantly greater in patients with PA and secondary hyperaldosteronism than in healthy subjects [148].

Good control of office blood pressure does not necessarily indicate good control of home or nocturnal blood pressure. Hence, blood pressure control should also be evaluated by ambulatory blood pressure if applicable. Specific treatment of PA with MRAs could significantly improve ambulatory blood pressure [149].

Some of the patients with normal, high–normal, or elevated blood pressure meet the diagnostic criteria for PA [150]. Although these patients may not be indicated for antihypertensive medications if based on the guideline for EH [7], they exhibited an increased urinary potassium excretion and a decreased serum potassium level, suggesting MR activation [151]. In addition, patients with suppressed PRA (<0.5 ng/mL/h) are at an elevated risk of later development of hypertension [152].

Taking all these together, we recommend specific treatment with MRAs in PA patients, even under good blood pressure control and normal serum potassium concentrations. However, further evidence is needed to strengthen this recommendation since no randomized controlled trials have compared specific *versus* nonspecific medicines for PA patients with normal blood pressure and normokalemia, including their effects on long-term prognosis. Individualized medicine is warranted considering the overall benefits of specific treatments with MRAs and potential adverse effects such as excessive blood pressure fall.

CQ 21. What are the recommended medicines for female patients with PA who are pregnant or desire childbearing?

Point 1. We recommend treating hypertension with antihypertensive medicines approved for pregnancy (α-methyldopa, hydralazine, labetalol, and nifedipine only after 20 weeks of pregnancy) (1B).

Point 2. We recommend treating hypokalemia with potassium preparation (1B).

Point 3. We suggest using MRAs if the treatment benefits are expected to outweigh the risks in patients with uncontrolled hypertension and hypokalemia under conventional treatment (2D).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

There is limited evidence regarding medications for female patients with PA who are pregnant or have a plan for childbearing. The guideline from the Japan Society of Hypertension for the management of hypertension and the guideline from the Japan Society for the Study of Hypertension in Pregnancy recommend the following antihypertensives for gestational hypertension: α-methyldopa, hydralazine, labetalol, and nifedipine (only after 20 weeks of gestation) [7, 153]. These medicines can be used safely, even for hypertension in patients with PA. The 2017 guidelines for obstetrical practice in Japan indicated that calcium channel blockers, including nifedipine, nicardipine, and amlodipine, have no adverse effects on the fetus when taken during early gestation [154]. The Japan Society of Hypertension guideline stated that nifedipine is acceptable before 20 weeks of gestation after obtaining adequate informed consent when alternative medicines are unavailable [7].

In several case reports of pregnant patients with PA who took MRAs, no adverse events associated with the MRAs were demonstrated [155-157]. However, the safety of MRAs, the differences in efficacy, and the adverse effects of the three MRAs in pregnant patients with PA with severe hypertension and severe hypokalemia remain unclear. In animal experiments, SPL, which has a more significant anti-androgen effect than EPL and ESA, impaired gonadal development [155, 156]. The use of SPL, particularly during early gestation, should be avoided. Some reports demonstrated successful delivery after laparoscopic adrenalectomy during the early second trimester (14 weeks 0 days to 27 weeks six days) in PA patients with uncontrolled blood pressure and hypokalemia and a unilateral adrenal adenoma on MRI [156, 157].

The treatment principles for pregnant patients with PA are the control of hypertension with recommended antihypertensive medicines for pregnancy and normalization of hypokalemia with potassium preparation. We suggest MRAs or adrenalectomy as treatment options in patients with uncontrolled hypertension and hypokalemia after carefully considering the benefits of overweighing the risks and adequate informed consent.

CQ 22. What kind of antihypertensive medication is recommended in patients with a positive PA screening test who do not want to undergo further examination?

Point 1. We suggest antihypertensive medicines, including MRAs, in patients with a positive PA screening test who do not want to undergo a confirmatory test (2C). We recommend MRAs in patients with typical clinical findings suggesting PA (1B).

Point 2. We recommend conventional antihypertensive medicines in patients with hypertension who showed negative confirmatory tests (1A). Since the possibility of PA is not entirely excluded in these patients, careful follow-up is recommended (2C).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

Patients with a positive PA screening test who do not want further examination comprise PA patients and non-PA patients. Although the prevalence of PA in the screening positive patients varied among studies [158-160], PA patients would benefit from MRAs as the first-line medicine for PA (see CQ 17). We, therefore, suggest antihypertensive drugs, including MRAs, in patients with a positive PA screening test who do not want to undergo a confirmatory test [4, 7]. We recommend MRAs in patients with typical clinical findings of PA where the confirmatory test could be bypassed [66] (see CQ 7, CQ20). However, no study has established enough evidence to show that MRAs are more effective than other antihypertensive drugs for non-PA hypertensive patients who showed a positive PA screening test. Treating non-PA hypertensive patients with MRAs needs consideration for possible adverse effects such as hyperkalemia and hyponatremia.

When PA confirmatory test is negative, the patients need appropriate antihypertensive treatment as EH [6]. However, false-negative results in the confirmatory tests do not entirely exclude the diagnosis of PA [60, 161, 162]. In addition, other causes of secondary hypertension, including sleep apnea syndrome, Cushing syndrome, and pseudoaldosteronism, show positive screening results occasionally. We suggest careful follow-up and periodic re-evaluation in the patients with a positive screening test where confirmatory tests were not performed or showed negative results.

CQ 23. Is there a difference in prognosis between adrenalectomy and medical treatment with MRAs in patients with unilateral PA?

Point 1. Adrenalectomy is superior to MRAs in antihypertensive effects (B). Adrenalectomy is as good as or better than MRAs in correcting hypokalemia, preventing the progression of target organ damage, and improving life prognosis (B).

MRAs, mineralocorticoid receptor antagonists

Evidence and comments

Adrenalectomy was superior to MRAs in improving blood pressure, hypokalemia and reducing the defined daily dose (DDD) of antihypertensive medicines six months after specific treatment [77]. However, there was

no superiority to MRAs in the Elderly [163]. Studies of longer-term prognosis in Italy (mean follow-up period: 21 months) and Singapore (mean follow-up period: 5.7 years) demonstrated that the adrenalectomy was superior to MRAs in improving blood pressure and reducing DDD, whereas there was no difference in the improvement of hypokalemia [164, 165]. According to a study using the medical insurance database in Taiwan (mean follow-up period: 5.8 years), the incidence of cardiovascular events and all-cause mortality after matching the prevalence of coronary artery diseases and cerebrovascular diseases were significantly lower in the adrenalectomy group than the MRAs group [166]. Adrenalectomy also improves QOL and prevents the onset and the progression of impaired glucose tolerance [167]. In contrast, there are conflicting results regarding the differences between the two treatments for improving renal prognosis and cardiac function [135].

Adrenalectomy can yield clinical outcomes equal to or better than MRAs in the majority of the patients [128], while medical therapy needs continuation for a lifetime. Therefore, adrenalectomy is the first-choice treatment in patients with unilateral PA, although we suggest a careful indication of surgical treatment in the Elderly. Alternatively, MRAs are the first choice for patients with unilateral PA who are unable or unwilling to undergo adrenalectomy [168] (see CQ 17)

CQ 24. What are the factors that affect the therapeutic outcome and prognosis after adrenalectomy?

Point 1. The cure rate of hypertension by adrenalectomy in patients with unilateral PA is affected by the number of antihypertensive medicines before surgery, the duration of hypertension, gender, BMI, age, and renal function (B).

Point 2. A decrease in eGFR in the early stage after adrenalectomy predicts a favorable outcome in the long-term renal function (C). A high PAC and hypokalemia are significant predictors of the initial decrease in the eGFR after adrenalectomy (C).

Point 3. Hyperkalemia may develop and persist for an extended period after adrenalectomy, requiring periodic follow-up and appropriate treatment. (1C)

eGFR, estimated glomerular filtration rate

Evidence and comments

Therapeutic effects of adrenalectomy are judged by two aspects: clinical cure (complete clinical success) indicating a normalization of hypertension and biochemical cure indicating a normalization of the aldosterone excess [128]. The clinical cure rate was 50.6% in a study of meta-analysis (n = 4,000) [169] and 32.6% in the JPAS in Japan (n = 574) [170]. A lower number of antihypertensive medicines, a shorter duration of hypertension before adrenalectomy, female gender, and low BMI were the factors for better clinical cure [170]. A single-center study in Japan (n = 142) demonstrated that younger age and higher eGFR were important predictors of clinical cure after adrenalectomy [171].

A single-center study in Japan has demonstrated that the eGFR decreased by 19.7% at six months after adrenalectomy for unilateral PA. A high PAC, hypokalemia, and high eGFR before adrenalectomy were factors contributing to this eGFR decrease [172]. Another single-center study in Japan has demonstrated that hypokalemia and albuminuria were independent predictors of the initial decrease in eGFR after adrenalectomy [23]. However, in the JPAS cohort, the initial decrease in eGFR predicted a favorable outcome in the long-term renal function [24].

Hyperkalemia is also an adverse effect after adrenalectomy, needing careful monitoring and appropriate management (see also CQ 18 and its evidence and comments)

Perspectives

Cause of PA

Recent studies extensively investigated the molecular characteristics of APA. Approximately 1–5% of all PA cases are familial hyperaldosteronism (FH), characterized by four different forms, FH-1 to 4. A chimeric CYP11B1/CYP11B2 gene causes FH-1; a germline mutation in the voltage-gated chloride channel two genes causes FH-2; a germline mutation in the inwardly-rectifying potassium channel subfamily J member five genes (*KCNJ5*) causes FH-3, and a mutation in the voltage-gated calcium channel subunit alpha1 H causes FH-4. A somatic mutation in *KCNJ5* causes approximately 30–60% of the sporadic form of APA [173]. This mutation is closely related to specific DNA methylation [174] or microRNA expression [175] and, significantly, to the clinical outcome of adrenalectomy [176]. Thus, identifying the circulating biomarkers of these genetic mutations will be clinically crucial for subtype diagnosis and surgical indications. Furthermore, the development of somatic mutation-specific treatments is expected.

Issues on the method for measuring aldosterone concentrations

Several changes in the assay methods of aldosterone and reference values have impacted the diagnosis of PA in clinical practice. Although PAC has been measured by RIA in Japan, production of RIA kits was discontinued in April 2021, and 3 CLEIA kits are currently used to measure PAC. Since the values by CLEIA are signifi-

cantly lower than those by RIA, borderline ranges were set for ARR and PAC and provisionally designated to be positive results. Optimal cut-off values of ARR and PAC for screening and confirmatory tests must be verified [37-39, 177].

Issues on screening tests

Difficulties in accurate quantification of renin in the low range, and false-positive results derived from a significant influence of renin as the denominator are the problems of ARR. Thus, we recommend adopting the PAC and the ARR to ensure hyperaldosteronism for PA screening, complicating screening indicators through duplicate use of PAC. Since the sensitivity and specificity of PAC and renin measurements have improved dramatically, it will be necessary to set optimal cut-offs for both PAC and renin and use them individually instead of the ARR for screening.

Issues on the confirmatory tests

Confirmation of the autonomous aldosterone secretion is essential for the diagnosis of PA. However, the guidelines recommend several confirmatory tests, and the cut-off values for the positive results remain to be standardized, which are responsible for the increased number of tests and the heterogeneity of PA diagnosis. Establishing a single confirmatory test that is easy to carry out and has few complications is necessary. In addition, the cut-off for the confirmatory test needs reassessment. 'Non-PA' hypertensive patients are used as a control group to set the cut-off for confirmatory tests. However, the diagnosis of 'non-PA' is based on the negative results in the confirmatory test with the specific cut-off reported previously. There exists a circular logic in this issue. The extent to which PA should be diagnosed in patients with mild aldosterone excess, generally bilateral, needs to be re-examined from the perspective of long-term prognosis. The cut-off for positive results of confirmatory tests needs review, focusing more on the specificity of the diagnosis of unilateral PA for adrenalectomy.

Future perspectives on PA subtype and laterality diagnoses

Non-invasive subtype testing

Steroid profiling by LC-MS/MS has been an alternative to AVS for classifying the PA subtype. As 18-oxocortisol and 18-hydroxycortisol are increased explicitly in APA harboring the *KCNJ5* mutation, which is frequent in Asian patients, the clinical application of these markers in subtype testing is expected [178, 179]. Most PAs recently diagnosed in Japan are mild cases with normal serum potassium concentrations, a mild degree of PAC elevation, no nodules on CT, and bilateral subtype by AVS [16, 85]. Therefore, further investigation to improve the diagnostic accuracy of subtype prediction based on non-invasive clinical findings will lead to the stricter application of AVS in mild PA likely to be bilateral.

Non-invasive imaging diagnosis

Given that AVS has various limitations that could interfere with its versatility and standardization, including technical difficulty, invasiveness, and limited facilities that can employ this method, it is essential to develop non-invasive imaging diagnostic methods. Although 11C-metomidate/PET targeting CYP11B is reportedly helpful for PA subtype diagnosis [180], clinical application of this method is problematic due to the short half-life of 11C and the need for pretreatment with dexamethasone to block the binding of the isotope to cortisol-producing CYP11B. The expression of chemokine receptor 4 (CXCR4), a receptor for inflammatory cytokines, is increased in aldosterone-producing tissue (particularly adenomatous tissue) and is well correlated with the expression of CYP11B2. 68Ga-pentixafor PET/CT targeting CXCR4 is useful for determining the classification and lateralization of PA [181]. In addition, a CYP11B2-specific imaging agent has been developed [182]. Non-invasive imaging diagnosis requires excellent sensitivity, specificity, and cost-effectiveness as an AVS alternative.

Current issues with AVS

AVS has been in use for more than 45 years to classify the PA subtype. There was a time when adrenal CT and adrenal scintigraphy replaced AVS as the first choice for subtype testing of PA. However, the diagnostic significance of AVS was reassessed in terms of the diagnosis of microadenomas without clear adrenal tumors on CT and the exclusion diagnosis of non-functional adenomas. Increased experience and various approaches improved success rate, safety, and efficacy, making it a gold standard for the subtype diagnosis. However, the AVS as a gold standard for subtype testing needs further improvement. First, based on the analysis of postoperative outcomes, it is necessary to standardize the method, including the pros and cons of ACTH stimulation, and establish the optimal criteria for the subtype testing. Second, it is necessary to reduce further the burden on patients in terms of time required, radiation exposure, and complications. One study demonstrated that segmental AVS, involving blood sampling from several tributaries of the adrenal vein, helps improve the accuracy of laterality diagnosis [183]. However, further evidence, including diagnostic ability, accuracy, safety, the time required for the procedure, versatility, cost-effectiveness, and long-term postoperative outcome, is needed to

justify the more extensive application of the modified AVS method.

Pathological diagnosis of PA using immunohistochemistry

The development of antibodies targeting CYP11B2, which is crucial for aldosterone biosynthesis, has enabled the pathological detection of aldosterone-producing lesions by immunohistochemistry. An international consensus on the pathohistological diagnosis of PA has classified four pathological subtypes (APA, aldosterone-producing nodules or aldosterone-producing micronodules, multiple aldosterone-producing nodules or micronodules, and aldosterone-producing diffuse hyperplasia) [184]. Further studies are needed to show whether the immunohistochemistry of CYP11B2 helps determine treatment strategies and predict clinical outcomes after adrenalectomy.

Therapeutic challenges

Antihypertensive treatment of patients with a positive screening test but negative confirmatory test for PA

We should treat hypertensive patients with a positive screening test but negative confirmatory test for PA as non-PA hypertension with the appropriate antihypertensive medicines. Whether MRAs are the first choice depends on the pathophysiological significance of the very mild aldosterone excess in these non-PA patients. The concept of mineralocorticoid receptor-associated hypertension has been proposed [185], but insufficient evidence as an independent disease entity. The MRAs could be effective in patients with hypokalemia and resistant hypertension. For the recommendation of MRAs in patients with normal serum potassium concentrations and good blood pressure control, it is necessary to conduct clinical trials to compare the effects of MRAs and other antihypertensive medicines on the development of organ damage and prognosis.

Contraindication for the concurrent use of potassium supplements with MRAs

When hypokalemia associated with aldosterone excess is severe, it is difficult to control the serum potassium concentrations with MRAs alone. However, the concurrent use of potassium preparation with EPL or ESA is a contraindication in Japan. SPL is usually used in such cases, but it has sex-hormone-associated adverse effects, particularly in male patients. Furthermore, SPL use was an independent predictor of a more significant eGFR decrease in female patients [147]. Given that there is a clinical need for concurrent EPL or ESA with potassium preparation in severe hypokalemia in PA, it is mandatory to accumulate evidence for the safety and efficacy of the combination for future approval.

New interventional techniques

Although laparoscopic adrenalectomy is the standard surgical treatment for APA, various treatments have been developed for reducing invasiveness: minimally invasive partial adrenalectomy [186], robot-assisted partial adrenalectomy [187], radiofrequency ablation for adrenal adenomas [188], and adrenal artery ablation [189], respectively. These new techniques are expected as an alternative treatment when patients have no desire for surgery or under general anesthesia is not indicated. However, given the well-established safety and effectiveness of laparoscopic adrenalectomy, critical and long-term verification of the safety and efficacy of these 'non-surgical techniques' is required before its more common clinical application.

Conclusions

Fig. 1 shows the algorithm developed for the clinical practice of PA in the 2021 guideline. Fig. 2 illustrates the positive decision criteria of the screening and confirmatory tests. Based on the evidence from studies published in peer-review journals, we have compiled the most standard answers to the major CQs, considering the framework of the medical insurance system, cost-effectiveness, and expert opinions. Consistency with existing guidelines and comments from related academic societies were also incorporated. We put maximum effort into maintaining the objectivity of the consensus process and recommendations following the MINDS manual for Guideline Development 2017. Creating clinical practice guidelines is a significant task that requires a great deal of effort and cost. In addition, the COVID-19 pandemic affected the process of compiling and developing this guideline, especially the consensus process, by limiting regular activity among the task force members and hampering direct discussions of the complicated issues. We however believe that this clinical practice guideline will contribute to promoting national health by improving the quality of PA medical care.

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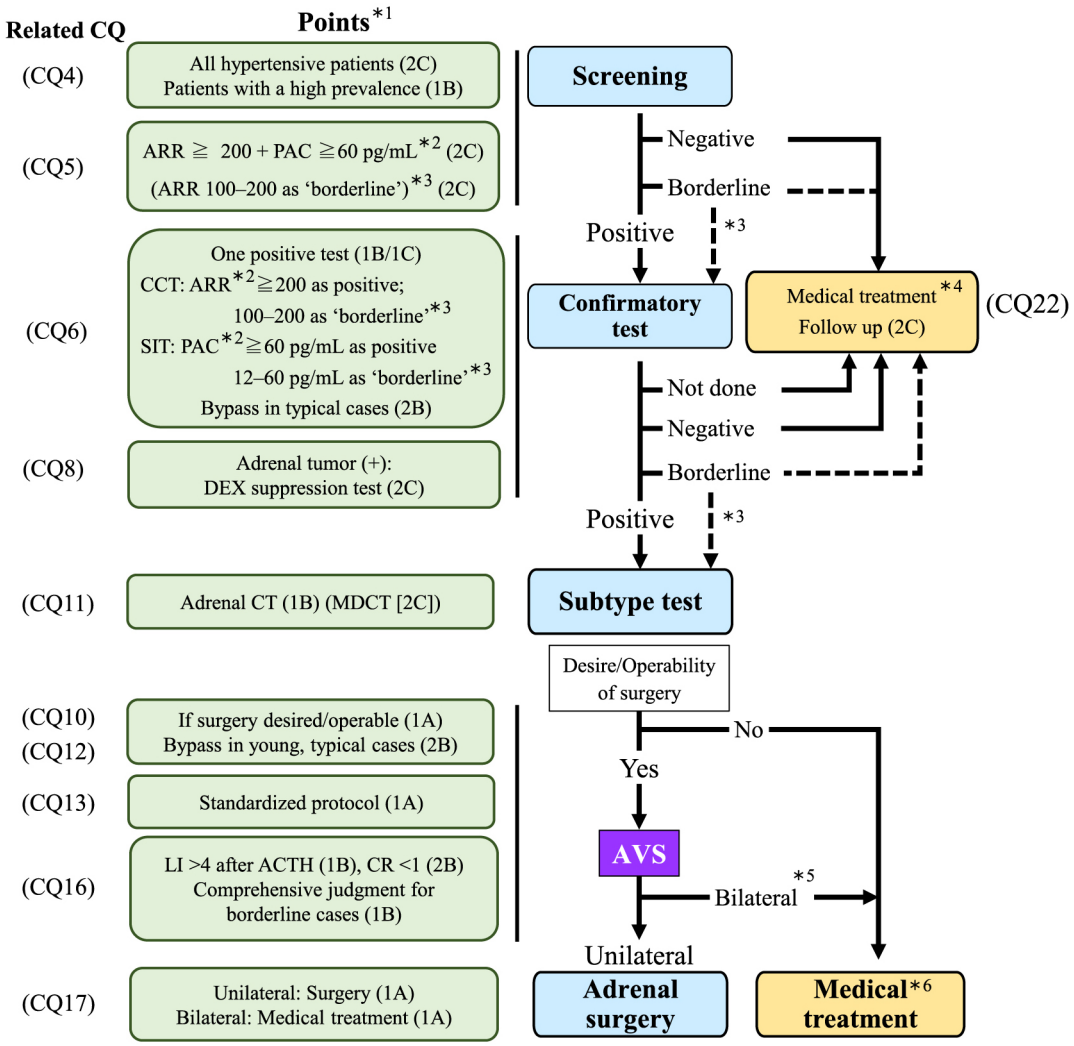

Fig. 1 Algorithm of the clinical practice of PA in Japan.

*1 Strength of recommendation and evidence in parentheses.

*2 PAC by CLEIA methods.

*3 Results in the borderline ranges are provisionally designated as positive. Diagnostic procedures and treatment should be determined individually by considering each patient's need and clinical findings.

*4 MRAs recommended in patients with typical findings of PA (1B).

*5 Consider adrenalectomy in bilateral patients if medical treatment is ineffective (2C).

*6 Treatment with MRAs as the first-line medicine (1A).

ARR, aldosterone to renin ratio; CCT, captopril challenge test; CQ, clinical question; CR, contralateral ratio; DEX, dexamethasone; LI, lateralization index; MDCT, multidetector-row computed tomography; PAC, plasma aldosterone concentrations; SIT, saline infusion test

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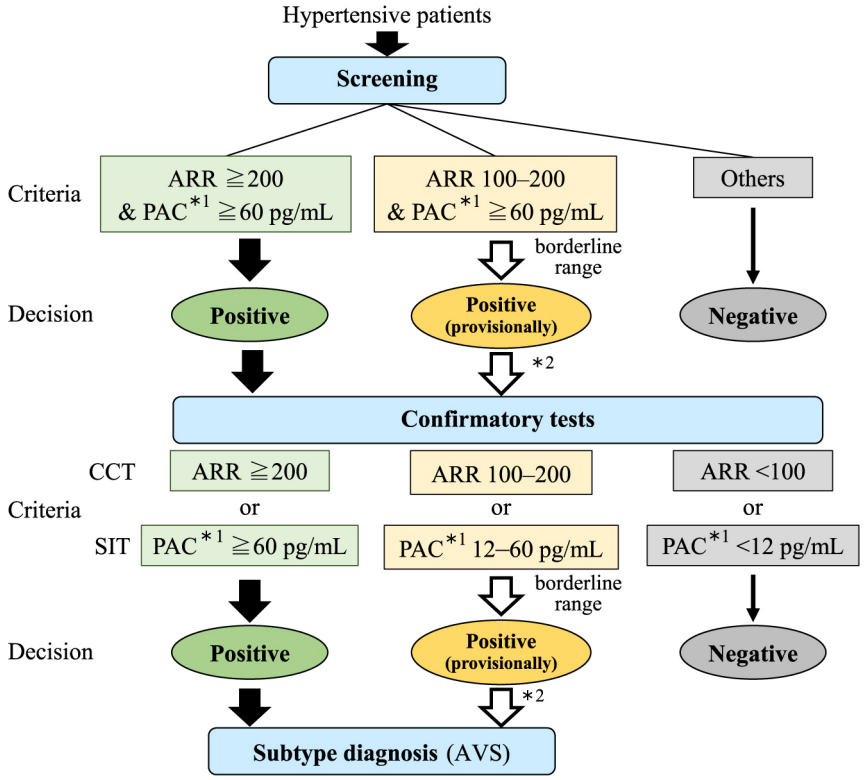

Fig. 2 Positive decision criteria of the screening and confirmatory tests in the diagnosis of PA.
*1 PAC determined by CLEIA methods
*2 Next step of diagnosis and treatment should be decided in the individual patient based on the patient's desire and clinical findings.
ARR, aldosterone to renin ratio; AVS, adrenal venous sampling; CCT, captopril challenge test; PAC, plasma aldosterone concentrations; SIT, saline infusion test

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This clinical practice guideline summarizes what is standard at present concerning domestic and foreign academic manuscripts, domestic clinical practice, and expert opinions regarding the clinical practice of PA. Therefore, it is necessary for physicians in charge of medical treatment to consider the conditions of individual patients and the situation of each medical facility and utilize the guideline realistically and flexibly. The guideline does not naturally constrain individual medical care. Although the responsibility for the contents of this clinical practice guideline lies with the Japan Endocrine Society, the responsibility for medical practice lies with the medical care facility and the physician in charge of the patient. It is, therefore, necessary for physicians in charge to perform medical treatment in compliance with Japan's medical insurance system and domestic laws and regulations. The copyright of this clinical practice guideline belongs to the Japan Endocrine Society and the task force of the guideline.

Disclosure Statement

The disclosure of the members was summarized in the table with the name of the company and organization. The other members not listed had nothing to disclose.

Members	Patent royalties	Speaker fees	Research funding	Scholarship donations	Endowed chair
M.N.	—	19	30, 39, 42	—	—
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M.S.	—	2, 19	—	3, 8, 21, 29	6, 8, 23
A.T.	—	—	8	—	—
S.I.	—	—	—	3, 7, 8, 10, 12, 17, 18, 19, 22, 23, 26, 28, 31, 32, 33, 35, 38	—
T.I.	—	—	19	—	—
M.O.	—	19	1	—	—
T.O.	—	32	—	—	—
I.K.	—	19	—	—	—
F.S.	—	8, 19	—	19, 21, 22	6, 8, 12, 20, 29, 48
T.T.	—	—	44	8, 19, 34	13
K.T.	—	2, 12, 19, 22, 21, 29, 32, 41	2, 8, 9, 25, 45, 47	1, 6, 7, 11, 19, 22, 26, 27, 34, 36, 41, 47	—
H.H.	—	—	—	5, 15, 16, 33	—
K.Y.	—	19	—	1, 4, 9, 19, 20, 21, 22, 23, 26, 29, 32, 34, 36	—
H.R.	—	6, 19, 22	14, 26, 46	1, 6, 9, 19, 21, 22, 23, 26, 29, 32, 34, 41	—

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