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Diagnosis and Management of Primary Aldosteronism: the Endocrine Society guideline 2016 revisited

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Abstract

The syndrome of primary aldosteronism (PA) is characterized by hypertension with excessive, autonomous aldosterone production and is usually caused by either a unilateral aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). The diagnostic workup of PA is a sequence of three phases comprising screening tests, confirmatory tests and the differentiation of unilateral from bilateral forms. The latter step is necessary to determine the optimal treatment approach of unilateral laparoscopic adrenalectomy (for patients with unilateral PA) or medical treatment with a mineralocorticoid receptor antagonist (for patients with bilateral PA). Since the publication of the revised Endocrine Society guideline 2016 a number of key studies have been published. They challenge the recommendations of the guideline in some areas and confirm current practice in others. Herein we present the recent developments and current approaches to the medical management of PA.

Introduction

Primary aldosteronism (PA), first described by Jerome W. Conn in 1955, was once thought to be a rare condition of hypertension characterized by hypokalemia and excess aldosterone production relative to suppressed plasma renin (1). The application of the current screening method of an elevated plasma aldosterone-to-renin ratio (ARR) to a wider target population (instead of restricted to patients with hypokalemia) accounting for up to 50% of the population with hypertension has greatly increased the diagnosis of PA (2). It is now widely accepted that this syndrome is the most common form of endocrine hypertension. PA is specifically treated by unilateral adrenalectomy (preferably by laparoscopic surgery) or pharmacologically with a mineralocorticoid receptor (MR) antagonist that competitively inhibits the binding of aldosterone to the MR (3).

Patients with PA have an increased risk of cardiovascular and cerebrovascular events and target organ damage (heart and kidney) relative to patients with essential hypertension and a matched cardiovascular risk profile (4-7) or compared with the general population with hypertension (8). Patients with PA also display an increased prevalence of metabolic syndrome and diabetes (4, 9-11), osteoporotic fractures (12) and symptoms of depression with a reduced quality of life (13-14). Some of these comorbidities may be associated with cortisol co-secretion (15). All available evidence indicates that an early diagnosis and appropriate clinical management (surgical or medical) is mandatory to minimize the increased risks associated with PA (5, 16-18).

The diagnostic management of PA comprises three phases: screening tests, case confirmation and differentiation of unilateral from bilateral forms of PA for therapeutic decision-making and appropriate treatment (Figure 1).

Diagnosis: Screening

Measurement of plasma aldosterone concentrations (PAC) and plasma renin activity (PRA) or the direct renin concentration (DRC) to assess the ARR is the most reliable currently available method of screening for PA. The Endocrine Society (ES) Clinical Practice Guideline recommends screening patients with an increased likelihood of PA (Table 1) (3). It has been suggested that all patients with hypertension should be screened for PA (19), based on the findings of the prospective PATO study (8) which reported a 5.9% prevalence of PA in 1672 unselected patients with hypertension in primary care (8). However, evidence that a systematic screening approach (compared with selective screening) results in a reduction of morbidity, mortality and cardiovascular disease of patients with hypertension to an extent that would justify the increased costs and burden on health systems is lacking.

To screen for PA by the ARR, it is recommended that medications interfering with the renin-angiotensin system, and specifically those that may stimulate renin secretion, should be withdrawn (this applies throughout the diagnostic workup for PA because other tests and procedures also rely on measurements of steroids under conditions of suppressed renin). Antihypertensive medication that interferes with the ARR includes diuretics (including spironolactone) and should be withdrawn for 4 weeks. Other drugs that should be withdrawn, but for a lesser period of 2 weeks prior to testing, are β-blockers, clonidine, methyldopa, non-steroidal anti-inflammatory drugs, ACE inhibitors, angiotensin receptor blockers and dihydropyridine calcium blockers (3, 20). However, in many instances, interpretation of the ARR is confidently possible without changing interfering medications. Non-dihydropyridine long-acting calcium channel blockers (verapamil or diltiazem), the vasodilator hydralazine and α1-adrenergic receptor blockers have limited or no effects on the ARR compared to the above and are suggested to control hypertension in those patients with elevated blood pressure requiring medical treatment (3, 20). As a caveat, severe deleterious side-effects have been reported by adjustment of antihypertensive therapy in accordance with the ES Guideline during screening for PA (21). In our center more than 90% of patients receive adjusted medication according to the ES guideline during screening, and serious adverse events have been reduced to a minimum after appropriate exclusion of high risk patients.

Before performing the ARR screening test, patients should avoid a low salt diet and have a minimum intake of 5g NaCl/day. Hypokalemia, if present, should be corrected. To allow activation of the renin-angiotensin system, blood samples are withdrawn in the morning when patients have been out of bed for ≥ 2 h. The assay characteristics and the use of different available commercial assays for the measurement of PAC, PRA or DRC can highly influence the ARR (22). The method-dependence of aldosterone and renin measurements has contributed to the lack of a standardized cut-off value for ARR screening and the wide variability in upper reference limits used across centers. The Japan ES Guidelines recommend a specific cut-off for the ARR (ARR > 200 with PAC in pg/mL and PRA in ng/mL/hr and indicate that the risk of PA increases with PAC > 120-150 pg/mL) with a specific commercially available assay (23). Radioimmunoassays are widely employed for the measurement of plasma PAC, PRA or DRC but assays using chemiluminescence have been shown to be reliable alternatives (24-26) using simultaneous assays for PAC and DRC (24).

An elevated ARR can result if the PRA (or DRC) is very low even if the PAC is low-normal and inconsistent with PA. Some centers do not proceed with the diagnostic workup of PA of such patients and require a minimum PAC in addition to an elevated ARR for a positive screening test. At least, baseline PAC should be higher than the normal range of confirmatory tests, as discussed later (20).

Diagnosis: Confirmatory Testing

Confirmatory testing is considered mandatory by the ES Guideline for a definitive diagnosis of PA. An exception is in evident cases of PA with spontaneous hypokalemia and a PAC > 20 ng/dL (550 pmol/L)] with PRA (or DRC) below assay detection limits (3). Confirmation or exclusion of the diagnosis of PA is performed by ≥1 confirmatory tests as recommended by the ES Guideline (3).

Confirmatory tests demonstrate the inappropriate production of aldosterone in response to exogenously administered agents that normally completely suppress or inhibit circulating angiotensin II levels (the endogenous positive regulator of aldosterone production). The test thereby confirms that aldosterone production is autonomous of the renin-angiotensin-system.

Potassium is a key regulator of aldosterone production and hypokalemia (if present) should be corrected with slow-release KCl tablets prior to confirmatory testing because failure to do so may produce a false-negative result. Since sodium chloride infusion during confirmatory testing may further deteriorate plasma potassium levels we administer KCl tablets even in patients with low normal potassium levels. Stress-induced increases of ACTH - indicated by an increase in plasma cortisol concentration - can interfere with aldosterone suppression and produce a false-positive test result. Consequently, cortisol levels should be monitored during confirmatory testing, and the aldosterone response interpreted with caution if increased cortisol levels indicate inappropriate stress at the end of the test.

The most commonly employed suppression tests use saline loading (either by intravenous infusion or orally), fludrocortisone (FST) or a captopril challenge (Table 2). Confirmatory testing based on saline loading are widely in use because they are straight forward and reliable and have low costs but saline loading by infusion (2 L i.v. infusion of 0.9% NaCl over 4h) or oral sodium intake (6g/day for 3 days, aldosterone measured in a 24 h urine collection over days 3 to 4) carry the risk of acute volume overload especially in those predisposed by left ventricular or renal dysfunction. The saline infusion test has a sensitivity of 83% using a cut-off of < 6.8 ng/dL (188 pmol/L) (27) and 88% using a cut-off of <5.0 ng/dL (<139 pmol/L) (28). A recent study suggested that up to 29% of patients with PA with suppressed aldosterone below 5.0 ng/dL (139 pmol/L) were patients with unilateral aldosteronism and candidates for surgery (29). The authors suggest that patients with an elevated ARR and elevated basal aldosterone concentrations may directly undergo AVS without a suppression test, a strategy also proposed in the recently published guideline for patients with hypokalemia (3). The sensitivity of the saline infusion test is reportedly increased by performing the test in the seated position (29-31). The captopril challenge test (25-50 mg orally administered captopril after sitting or standing for > 1 h) is likewise easily performed and circumvents potential fluid overload in patients who are at risk due to compromised renal or cardiac function. The FST requires the consumption of fludrocortisone with sodium and potassium supplementation and up to 5-days hospitalization to ensure control of blood pressure and plasma potassium concentrations that must be closely monitored throughout the test because of the risk of hypokalemia. Proponents of the FST highlight the safety of the test in expert hands with a superior sensitivity compared with other methods [a detailed protocol is described in Stowasser & Gordon (20)]. The test is nonetheless unfeasible in most countries because of cost limitations imposed by the requirement for several days' hospitalization.

Diagnosis: Subtype Differentiation

Subtype diagnosis begins with the exclusion of patients with a rare form of PA caused by an aldosterone-producing carcinoma using an imaging technique such as computed tomography (CT) scanning, or magnetic resonance imaging (MRI)]. The value of CT scanning and MRI have been questioned since they might not faithfully distinguish the source of aldosterone excess and micro-APAs (≤ 10 mm in diameter) are often undetectable by current imaging methods (32-33). In addition, the proportion of patients with adrenal incidentalomas increases with age leading to false positive imaging findings and reduced specificity. Therefore, the ES guideline issued a strong recommendation to perform AVS in every patient who is a candidate for surgery to reliably differentiate unilateral from bilateral PA.

Blood samples are obtained for steroid measurements from the right and left adrenal veins to determine if the overproduction of aldosterone originates from a unilateral or bilateral source (Figure 2). Some experts recommend AVS in all patients with confirmed PA (34), others consider predictors of unilateral disease and patient preference (35, 36). According to the ES Guideline, young patients (< 35 years) with imaging findings of a unilateral adenoma (> 10 mm and a normal appearing contralateral adrenal) can bypass AVS if they display a marked phenotype (for example, PAC > 30 ng/dL [831 pmol/L] and spontaneous hypokalemia at baseline) (3). Although selecting patients to bypass AVS and proceed to surgery on the basis of young age, imaging results and PA phenotype has been reported to lack specificity (37), data from a multicentric study in Japan reported that factors based on young age and specific imaging and biochemical characteristics as recommended by the ES guideline could accurately predict unilateral disease (38).

In preparation for AVS, antihypertensive medication that interferes with the renin-angiotensin system, specifically by stimulating renin secretion, should be withdrawn. Loop and thiazide diuretics, amiloride, and MR antagonists should be interrupted 4 weeks before AVS and substituted for antihypertensive medication with less (or minimal) effects on renin secretion such as α1-adrenergic receptor blockers and non-dihydropyridine long-acting calcium channel blockers (verapamil or diltiazem). If plasma renin activity or concentration is suppressed, AVS can be performed irrespective of the time of drug withdrawal (39) and, in exceptional cases, MR antagonist therapy can be continued during AVS if renin remains suppressed (40).

The success of AVS, determined by the correct cannulation of the adrenal veins, is measured by the selectivity index (SI) which is calculated as the ratio of cortisol in the adrenal vein and in a peripheral vein. The cannulation of the adrenal veins is particularly challenging on the right side because of anatomical differences between the right and left adrenal veins (Figure 2). Success rates differ greatly but can be improved by a rapid cortisol assay to ascertain when resampling is necessary if the AVS was unsuccessful (41, 42). The use of such an assay has increased the proportion of successful AVS from 55% to 85% in the experience of one referral center largely due to an increased successful cannulation of the right adrenal vein (43). The lateralization of aldosterone production is usually calculated by the lateralization index (LI) although the LI is sometimes considered together with a requirement for contralateral suppression of aldosterone production to define lateralization (Table 3, Table 4). There is no standardized cut-off for the SI, or indeed for any of the indices used in AVS. Although there have been attempts to standardize AVS protocols (39, 44), the reference limits remain arbitrary to some extent and the interpretation of AVS results vary widely across centers (Table 4).

AVS is performed in the morning when ACTH-stimulated aldosterone production is maximal following at least 1 h recumbency to avoid the effects of postural changes on the stimulation of the renin-angiotensin-system. An AVS procedure with an exogenously administered synthetic derivative of ACTH (ACTH 1-24, called cosyntropin) is used by some for various reasons that include increasing technical success rates, stimulating the production of aldosterone from APAs and minimizing variations in cortisol and aldosterone production caused by stress-induced ACTH release during non-simultaneous AVS. Although some concerns have been raised on the possible stimulation of aldosterone production from the contralateral adrenal gland (non-dominant gland) in unilateral PA, AVS with ACTH infusion can improve the technical success rate of AVS (45, 46) and can perform as well as unstimulated protocols with ACTH administered as a bolus (usually 0.25 mg [10 IU]) or continuous infusion (initiated 30 min before the procedure [50 μg/h]) performing equally well (47). The effects of ACTH stimulation were illustrated by a study in which a bolus of 250 μg of ACTH increased bilateral selectivity from 67% in the basal state to 92% post-stimulation. At the same time, discordance between basal and post-ACTH values was observed in 28% of patients, which were mostly lateralized cases under basal conditions that became bilateral post-ACTH. Therefore, ACTH stimulation may reduce the proportion of lateralized PA. We observed no significant differences in the post-surgical clinical outcomes of patients with unilateral PA diagnosed by AVS with an unstimulated protocol (n= 331) relative to patients diagnosed with an ACTH infusion protocol (n=374) (48). In our center, we generally perform bilateral simultaneous AVS without ACTH stimulation. ACTH stimulation is restricted to specific situations: for example, if patients are at risk of an allergic reaction to the anesthetic, if AVS is performed in the afternoon and if patients receive chronic low-dose synthetic glucocorticoid treatment (i.e., 5 mg prednisolone/day).

The recently published SPARTACUS trial studied in a randomized fashion whether CT imaging based subtype determination was equivalent to AVS based decision making (49). The primary outcome of the study was the intensity of antihypertensive medication measured as defined daily drug dose (DDD) one year after initiation of specific treatment. Outcomes were essentially similar: the median DDDs of 92 patients receiving CT-based treatment (in 46 adrenalectomy and in 46 MRA treatment) was 3·0 versus 3·0 in those receiving AVS-based treatment (46 adrenalectomies and 46 treated by MRA, p=0·53). In the surgical groups, target blood pressure was reached in 39 (42%) patients and 41 (45%) of the operated patients, respectively (p=0·82). Additional secondary endpoints, such as health-related quality of life or biochemical remission (80% *versus* 89%, p=0.25), were not different. Details of the study and perceived weaknesses in its design and methodology have been discussed in an unprecedented and ongoing flood of commentaries (50-53) splitting the community into those who were for or against AVS. The emotions arising from the study are in part due to the trial highlighting that a sophisticated procedure such as AVS is not 100% accurate, having a failure rate of approximately 5% (48), and that CT based management might be better than previously thought. As a consequence of this debate centers who used AVS for therapeutic decision making will continue to do so but will likely exempt young patients with imaging-positive adenomas. Centers without access to AVS will base their decision making with increased confidence on CT imaging, acknowledging that this strategy might have a failure rate of up to 20% (49).

Treatment

The underlying cause of PA determines the appropriate treatment, surgical or medical management. For patients with unilateral PA, adrenalectomy offers the possibility of blood pressure remission or clinical improvement and the resolution of excess aldosterone production. In an international cohort study, unilateral adrenalectomy normalized blood pressure in 37% of 705 patients with PA and substantially improved the clinical outcome (blood pressure and antihypertensive medication response) in a further 47% (48). A successful biochemical outcome (correction of hypokalemia- if present pre-surgery- and normalization of the ARR) was achieved in 94% of 699 patients (48).

Patients with bilateral PA are most effectively treated medically with an MR antagonist, usually spironolactone (54). Other patients included in this category are those with unilateral PA who opt for medical rather than surgical management or those who are unfit for surgery. Cases of spontaneous complete biochemical remission have been reported in patients with bilateral PA after long-term treatment with MR antagonists in (2 of 37 patients treated with spironolactone [5.4%] at 10.8 and 12.9 years following diagnosis (55)] and in patients following long-term treatment with potassium canrenoate (56).

Spironolactone is a competitive inhibitor of aldosterone for its receptor, the MR. It is non-selective and displays both antagonist activity to the androgen receptor and agonist activity to the progesterone receptor. The non-selective action of spironolactone can cause the associated adverse effects including gynecomastia, erectile dysfunction and menstrual irregularities. The incidence of gynecomastia increases from <6.9% at a dose of <50 mg/day to 52% at >150 mg/day (57). Eplerenone is a selective MR antagonist that has no adverse effects but displays lower efficacy and high cost compared with spironolactone (58, 59). In Japan, eplerenone is approved for the treatment of hypertension, in the US and in Europe, for the treatment of congestive heart failure after a myocardial infarction.

A longitudinal study that included 602 patients with PA (treated with a MR antagonist) compared with 41,853 age-matched patients with essential hypertension treated conventionally demonstrated a significantly higher rates of cardiovascular events independent of blood pressure control in the PA group (60). Patients with PA also had higher adjusted risks for incident mortality, diabetes, and atrial fibrillation. The excess risk for cardiovascular events and mortality was limited to patients with PA whose renin activity remained suppressed (<1 µg/L per h) on MR antagonists. The study suggests that titrating the increase in plasma renin activity as a response to MR antagonist therapy instead of blood pressure control would be a more effective therapeutic approach to avoid the excess cardiovascular risk associated with PA (60). The PAPY study analysed long-term cardiovascular outcomes and mortality in 1125 patients screened for PA and treated according to biochemical results: unilateral adrenalectomy (4.8%) in patients with APA, MR antagonist treatment (6.4%) in patients with BAH and standard medical treatment in the remaining 88.8% with essential hypertension. After a median of 11.2 years overall survival was similar in patients treated for PA and for essential hypertension. MR antagonist treatment but not adrenalectomy was associated with a higher risk of atrial fibrillation (61). In summary, both studies raise the question of uptitrating the dose of MR antagonists to block the MR more effectively and reduce long-term complications.

Genetic forms of PA

A number of somatic mutations have been identified in ion channels and transporters that drive the aldosterone excess in patients with APAs (62, 63). No clinical application has been firmly established although a potential future use may lie in steroid profiling to circumvent AVS in patients with bilateral disease by selection of those patients with a high probability of having an APA (64) or by selecting patients with an APA carrying KCNJ5 mutations using macrolide antibiotics as selective inhibitors (65).

Germline variants have also been identified that cause rare familial forms of PA (62, 63). The invasive procedure of AVS is unnecessary in patients with Familial Hyperaldosteronism types I and III (FH type I and FH type III) (66, 67) because the former is effectively treated with glucocorticoids (such as dexamethasone) and the latter is treated by bilateral adrenalectomy or with MR antagonists. Therefore, in accordance with the ES Society Guideline (3), genetic testing is recommended in patients with a diagnosis of early-onset PA (< 20 years old) or with a family history of PA or stroke at a young age (< 40 years) for the presence of the hybrid *CYP11B1*/*CYP11B2* gene that causes FH type I (66) and in very young patients with a diagnosis of PA (for example, < 20 years) for germline mutations in the *KCNJ5* gene that cause FH type III (68). Genetic testing of patients in these target groups offers the possibility of an early diagnosis of asymptomatic relatives and provides timely treatment when appropriate. AVS should be performed in patients with Familial Hyperaldosteronism types II and IV (69-71) because these patients have been treated successfully by unilateral adrenalectomy as well as with MR antagonists (62). Germline heterozygous mutations in the voltage-gated chloride channel ClC-2, encoded by the *CLCN2* gene, have been identified in families with FH-II and in patients with sporadic childhood-onset primary aldosteronism (72, 73). ClC-2 is expressed in adrenal glomerulosa cells, and the mutated channels show gain-of-function with increased chloride conductance at resting potentials resulting in increased expression of aldosterone synthase and aldosterone secretion. These findings establish *CLCN2* mutations as a cause of early-onset primary aldosteronism.

Conclusions

Since the publication of the ES guideline on primary aldosteronism in 2016, several high quality reports have advanced our knowledge of the genetics, diagnosis, subtype differentiation and treatment of PA. In general, these data confirm the diagnostic and therapeutic algorithm of the guideline. An exception is the SPARTACUS study but an independent trial which takes into account the criticisms of the many commentaries will resolve the issue of the validity of the results. In addition, novel functional imaging methods of PA, such as CXCR4 PET-CT imaging (74), could offer an alternative to ease the subtyping of PA. In summary, accumulating evidence highlights the importance of an early diagnosis and indicates that specific treatments can minimize or reverse the adverse effects of aldosterone excess. However, simplified procedures are required to enable timely, cost-effective and patient-friendly screening and diagnosis for PA.

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FIGURE LEGENDS

Figure 1 Flow chart for the diagnostic workup of primary aldosteronism

* Please refer to Table 1 for patients with hypertension to be screened for PA

ADX, adrenalectomy; CT, computer assisted tomography; MR, mineralocorticoid receptor; PA, primary aldosteronism

Figure 2 Differentiation of Unilateral from Bilateral forms of Primary Aldosteronism by Adrenal Venous Sampling

Adrenal venous sampling is performed according to a defined standardized protocol in patients with confirmed PA after withdrawal of interfering medication (see text for details). Adrenal veins are sequentially catheterized via the femoral veins and blood is sampled from the inferior vena cava and from the right and left adrenal veins. The success of catheterization of each adrenal vein is indicated by the selectivity index (Tables 3-4) that can be determined by a rapid onsite cortisol assay (41-43). Plasma aldosterone and cortisol concentrations are measured in all blood samples. Adrenal venous plasma aldosterone concentrations are corrected for any dilution by blood from the inferior phrenic vein (on the left side) or from the inferior vena cava (on the right side) by dividing by the respective plasma cortisol concentrations (aldosterone-to-cortisol ratios). The measurements of aldosterone and cortisol are used to derive the lateralization index and the contralateral ratio (Table 3)

RISK GROUPS RECOMMENDED TO BE SCREENED FOR PRIMARY ALDOSTERONISM ACCORDING TO ES GUIDELINE
Patients with sustained blood pressure above 150/100 mmHg, grade 2 and grade 3 hypertension
Patients with resistant hypertension (blood pressure not controlled by 3 conventional drugs including a diuretic) or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs
Patients with hypertension and spontaneous or diuretic induced hypokalemia
Patients with hypertension and an adrenal incidentaloma
Patients with hypertension and sleep apnea
Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years)
All first degree relatives of patients with PA

Table 1 Screening for primary aldosteronism

Includes data from Funder JW et al. (3) and Stowasser M & Gordon RD (20)

CONFIRMATORY TEST	DIAGNOSTIC CUT OFF VALUES
Saline Infusion Test (SIT)	PAC > 5-10 ng/dL (140-280 pmol/L)
Oral Salt Loading Test (SLT)	uAldo > 12 μg/24h (33 nmol/d)* or > 14 μg/24h (39 nmol/24h)†
Fludrocortisone Suppression Test (FST)	Upright PAC > 6 ng/dL (170 pmol/L) on day 4 at 10 am with PRA < 1 ng/mL/h and plasma cortisol less than the value at 7 am‡
Captopril Challenge Test (CCT)	Decrease in PAC ≤ 30% (or ARR > 200 pg/mL/ng/mL/h)**

Table 2 Confirmatory testing for primary aldosteronism

PAC, plasma aldosterone concentration; PRA, plasma renin activity; uAldo, urinary aldosterone

* At the Mayo clinic;
† At the Cleveland clinic;
‡ To exclude any confounding effect of ACTH.
** Decrease in PAC ≤ 30% as defined by the ES Guideline (3) and ARR > 200 pg/mL/ng/mL/h by the Japan ES Guidelines (23).

Protocols describing confirmatory testing in detail are described in Stowasser and Gordon (20)

Includes data from Funder JW, et al. (3)

AVS INDEX	DEFINITION AND INTERPRETATION
Selectivity Index (SI)	$[Cortisol]_{AV}/[Cortisol]_{PV}$ *Indicates successful AVS with correct cannulation of adrenal veins*
Lateralization Index (LI)	$([Aldosterone]/[Cortisol])_{IpsilateralAV}/([Aldosterone]/[Cortisol])_{ContralateralAV}$ *Measures lateralization of aldosterone production*
Contralateral Ratio (CLR)	$([Aldosterone]/[Cortisol])_{ContralateralAV}/([Aldosterone]/[Cortisol])_{PV}$ *Inhibition of aldosterone production from the non-dominant adrenal gland* (contralateral suppression, CLR ≤ 1)

Table 3 Definition and interpretation of adrenal venous sampling criteria

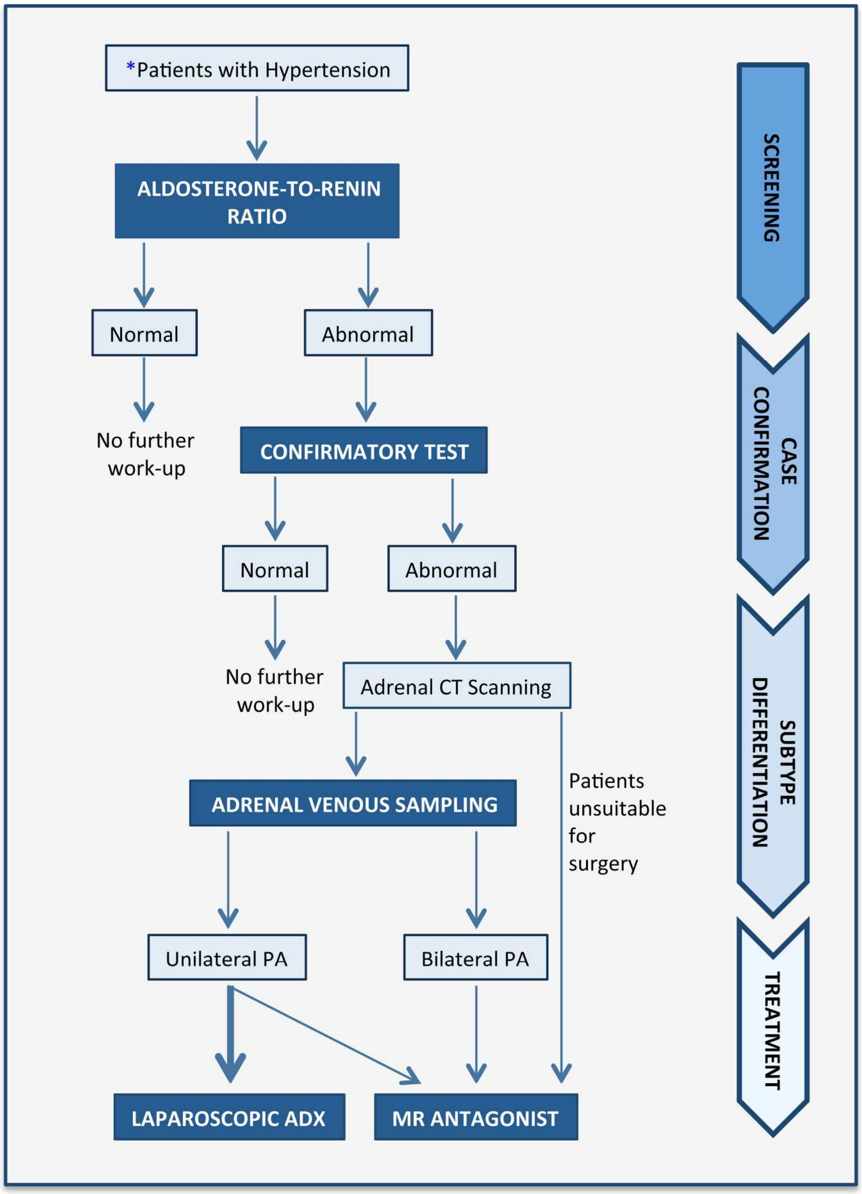
AV, adrenal vein; PV, peripheral vein (often the inferior vena cava); the ipsilateral AV is the adrenal vein from the adrenal with excess aldosterone production and the contralateral AV is the adrenal vein from the adrenal on the opposite side; AVS, adrenal venous sampling; ACTH, adrenocorticotropic hormone; PA, primary aldosteronism

REFERRAL CENTRE	UNSTIMULATED OR ACTH INFUSION	SUCCESSFUL AVS	DIAGNOSIS OF UNILATERAL PA
Munich Paris	Unstimulated	SI ≥ 2	LI ≥ 4
Torino	Unstimulated + continuous ACTH infusion	SI ≥ 3	LI ≥ 4 or LI ≥ 3 and CLR ≤ 1
Brisbane	Unstimulated	SI ≥ 3	LI ≥ 2.5 and CLR ≤ 1
Rochester	Continuous ACTH infusion	SI ≥ 5	LI ≥ 4
Sendai	Bolus ACTH infusion	SI ≥ 5	LI ≥ 2.6
Yokohama City	Bolus + continuous ACTH infusion	$[\text{Cortisol}]_{AV}$ > 200 μg/dL*	$[\text{PAC}]_{\text{ipsilateralAV}}$ > 1,400 ng/dL*

Table 4 Different protocols and interpretation of adrenal venous sampling

ACTH, adrenocorticotropic hormone; AVS, adrenal venous sampling; LI, lateralization index; PA, primary aldosteronism; PAC, plasma aldosterone concentration; SI, selectivity index. *In accordance with the Japan ES Guidelines (23)

Includes data from Williams TA, et al. (48)



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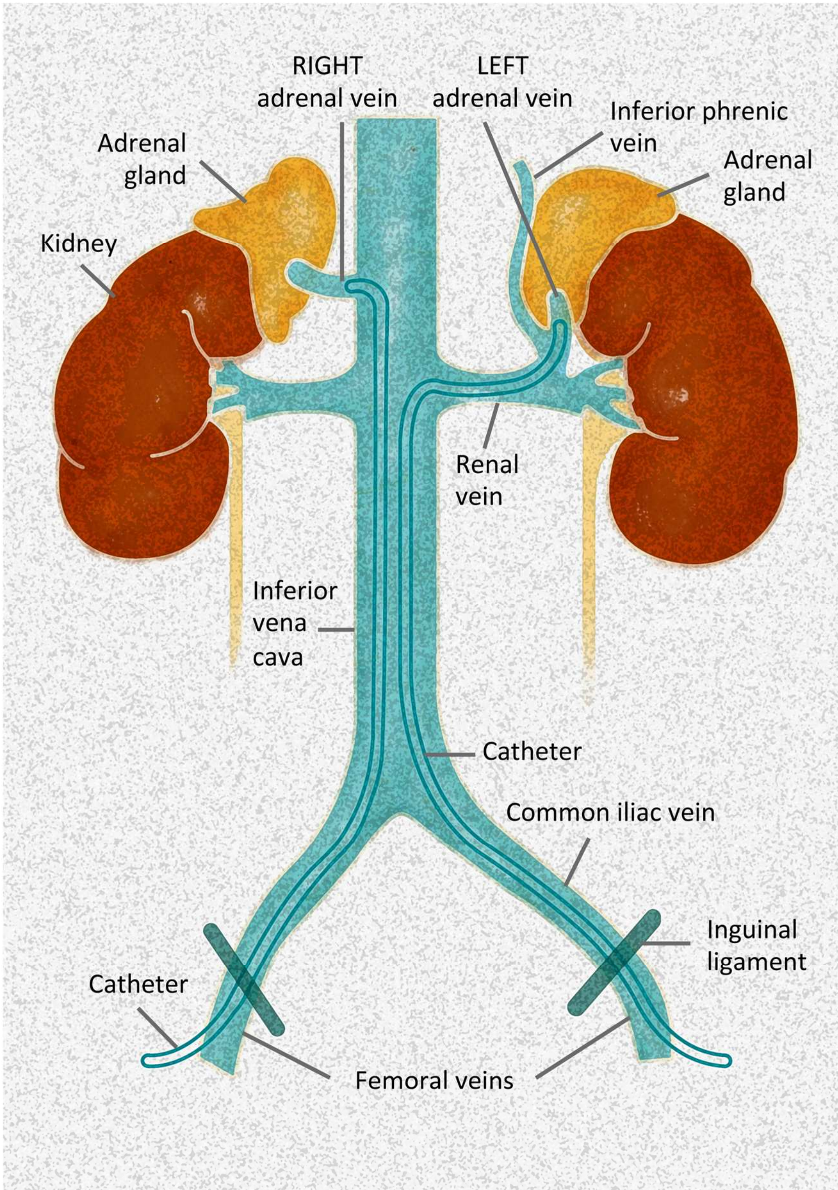

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