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Prevalence, Diagnosis and Outcomes of Treatment for Primary Aldosteronism

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Abstract

Primary aldosteronism (PA) is the most common potentially curable form of hypertension. The overproduction of aldosterone leads to an increased risk of cardiovascular and cerebrovascular events as well as adverse effects to the heart and kidney and psychological disorders. PA is mainly caused by unilateral aldosterone excess due to an aldosterone-producing adenoma or bilateral excess due to bilateral adrenocortical hyperplasia. The diagnostic work-up of PA comprises three steps: screening, confirmatory testing and differentiation of unilateral surgically-correctable forms from medically treated bilateral PA. These specific treatments can mitigate or reverse the increased risks associated with PA. Herein we summarise the prevalence, outcomes and current and future clinical approaches for the diagnosis of primary aldosteronism.

A) Introduction

Primary aldosteronism (PA) is an endocrine form of hypertension first described by Jerome Conn in 1955 in a young woman with an adrenocortical adenoma [1]. The characteristic features of PA are hypertension, overproduction of aldosterone and suppressed plasma renin. Once thought to be a rare disease with hypokalaemia a requisite for pursuing diagnostic work up, it is now widely accepted that PA is the most common form of endocrine hypertension with the majority of patients displaying normokalaemia [2]. Patients with PA have an increased risk of cardiovascular and cerebrovascular events, heart [3-8] and renal disease [7,9-13], diabetes, metabolic syndrome [8,14-17] and a reduced quality of life [18-21]. These observations highlight the importance of an early diagnosis and appropriate treatment of PA which can reversed by specific surgical or medical treatment.

The aldosterone excess originates from one or both adrenal glands (unilateral or bilateral PA) and may be caused by germline variants or arise sporadically [22,23]. The sporadic forms of PA predominate causing over 95-99% of all diagnosed cases of PA and are mainly due to a unilateral aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia (BAH, also called idiopathic hyperaldosteronism) [23]. Rarer forms of sporadic PA include unilateral adrenal hyperplasia (or primary adrenal hyperplasia) and the very rare aldosterone-producing carcinomas [24].

The optimal treatment for patients with unilateral PA is laparoscopic unilateral adrenalectomy, patients with bilateral PA are usually treated medically with a mineralocorticoid receptor (MR) antagonist. It is therefore essential that unilateral surgically-treatable forms of PA are accurately differentiated from bilateral PA. The recommended approach to differentiate unilateral from bilateral PA and to identify the adrenal for surgical resection is adrenal venous sampling (AVS) [25] although computed tomography (CT) is more widely used mainly due to technical difficulties and associated costs of AVS. The Endocrine Society clinical practice guideline for the management

of PA recommends three phases in the diagnostic work up of PA which comprise screening, confirmatory testing, and subtype differentiation [26].

B) Prevalence

Following the initial clinical description of PA, additional cases of PA were rapidly recognized [27]. At that time, PA was considered a rare disease comprising < 1% of patients with hypertension [28]. A screening test for PA was developed to measure the plasma aldosterone-to-renin ratio (ARR) [29] and the wider application of this screening test to include normokalaemic patients with hypertension in addition to those with hypokalaemia [30-32] resulted in a 5-15 fold increase in detection rates [2].

Prevalence of PA in populations with hypertension

Considerable variations have been reported in estimates of the prevalence of PA in populations with hypertension, partly due to the heterogeneity of the investigated population [33]. The prevalence of PA in the general population with hypertension was estimated as 2.6-12.7% [7,30,34-43], increasing with the severity of hypertension [7,35] and rising to 20% in patients with resistant hypertension [44]. Studies which assessed the incidence of PA according to hypertension grade reported a prevalence of 2.0-6.6% in grade I hypertension, 8.0-15.5% in grade II, and 11.8-19% in grade III [7,35,45]. The PATO (Primary Aldosteronism in TOrino) study prospectively screened a large cohort of 1672 unselected patients with hypertension in primary care using stringent diagnostic criteria and reported a prevalence of 5.9% of patients with a diagnosis of overt PA [7]. In the PATO study cohort, patients with bilateral disease comprised 65% of the total patients diagnosed with PA compared with 27% with unilateral PA; 8% had an undetermined subtype (unilateral *vs.* bilateral) because these patients either refused AVS or the AVS results were inconclusive [7]. The wide variance in the reported prevalence of PA in patients with hypertension in different studies is shown in Table 1.

In a study on screening for PA in 14 specialized hypertension centres, a conclusive diagnosis was made in 1125 of 1180 (95.3%) consecutively visited patients with hypertension. Unilateral APA was diagnosed in 54 of 1125 (4.8%) and BAH was found in 72 of 1125 (6.4%) patients. The use of AVS for subtype differentiation identified a higher prevalence of APA than BAH (62.5% vs 37.5%, P = 0.002) [45]. Käyser et al. [33] systematically reviewed 39 studies comprising 42510 patients with 36614 patients from hypertension units (26 studies) and 5896 patients from primary care 13 studies) and reported a prevalence of PA in hypertension referral centres ranging from 0.7% to 29.8% and from 3.2% to 12.7% in primary care. An additional 9 studies on the prevalence of PA in referred patients have since been published [33,46-54], bringing the median prevalence of PA in 55045 referred patients with hypertension in all 36 studies to date to 7.0%.

Prevalence of PA in special populations

The Endocrine Society Clinical Guideline recommends screening for PA in patients with hypertension and obstructive sleep apnoea (OSA) because this category of patients appears to display a particularly high incidence of PA [26]. In a study on newly referred patients with hypertension, 34% of 53 patients with moderate-to-severe OSA were diagnosed with PA compared with an estimated frequency of 10% among patients with hypertension without sleep disorders [55]. A similar prevalence of PA (diagnosed by an elevated ARR) of 30% of 343 patients with OSA was reported in another study which identified 343 OSA affected patients from 3428 patients with hypertension [56]. It should be noted that polysomnography was not used to confirm OSA in all patients in the above studies which were also not designed from the outset to investigate the frequency of PA in patients with OSA and hypertension, thereby limiting the interpretation of results. In an ongoing prospective study aimed to evaluate the prevalence of PA in OSA patients, a diagnosis of OSA was confirmed in 91 patients by polysomnography [57]. Of these, 20.9% of 91 patients were diagnosed with PA with a salt infusion test (SIT) compared with 7.3% (8 of 109) in

the group without OSA (P = 0.005). The incidence of PA was still relatively higher when patients with resistant hypertension were excluded. An elevated frequency of PA was shown in patients with increasing severity of OSA symptoms (severe *vs.* moderate OSA: 24.5% *vs.* 16.7%, P = 0.011) [57]. The positive correlation of PA and OSA in this prospective study underlined the necessity of screening for PA in patients with hypertension and OSA.

Jerome Conn was the first to report impaired carbohydrate tolerance in patients with PA [58]. Several studies have since reported a high rate of type 2 diabetes and metabolic syndrome coincident with PA [6,14,16,17,59]. PA accounts for a significant proportion of patients in diabetic populations with hypertension, ranging from 11.3% to 14% [60-62], compared with 0.93% in the general population with diabetes reported in a multicentre cross-sectional study which consecutively screened 578 patients [63]. Available data to date were acquired from studies with either small cohort sizes or varied study methodologies, therefore large-cohort prospective investigations are required for prevalence evaluations, and more importantly, to provide evidence to determine if patients with type 2 diabetes especially with hypertension should be systematically screened for PA.

The prevalence of PA in patients with adrenal incidentalomas has been evaluated in many studies, showing a median of 2% (range, 1.1-10%) [26], with a comparable prevalence in patients with unilateral and bilateral incidentalomas (4.3% vs 5.4%, P > 0.99) [64]. Therefore, the Endocrine Society Clinical Guideline recommends screening for PA in patients with incidentally discovered adrenal lesions [26].

C) Diagnosis

The higher prevalence of adverse effects in patients with PA relative to patients with EH highlights the importance for the early diagnosis of patients with PA including accurate subtype differentiation to assign the specific treatment option.

Screening test

Endocrine Society Clinical Practice Guideline recommends ARR screening test in patients with increased risks of PA: patients with resistant hypertension to ≥ 3 conventional antihypertensive drugs, hypertension and hypokalemia (spontaneous or diuretic induced), hypertension and an adrenal incidentaloma, hypertension and a family history of early-onset hypertension or cerebrovascular accident at age < 40 years, hypertension and sleep apnea, patients with sustained blood pressure > 150/100 mmHg, or all first-degree relatives of patients with PA [26]. In total, around 50% of the hypertensive population should be screened.

It has been suggested that all patients with hypertension should be screened for PA [65]. One supporting example was a 10-fold elevated diagnostic rate of PA achieved in several hypertension units in Australia applying such policy [66]. Similarly, an increased screening intensity programme in Germany resulted in a higher diagnosis of patients with mild symptoms [67]. However, to date there is no compelling evidence to show the benefits from systematic screening considering the associated costs and burden on health systems.

Before screening by the ARR test, if hypokalemia is present, it should be corrected to the normal range (around 4.0 mmol/L), and patients should be encouraged to liberalize sodium intake (≥ 5g NaCl/day) [26,68]. Antihypertensive medication including potassium-wasting or -sparing diuretics and products derived from liquorice should be withdrawn for 4 weeks. Two-week withdrawal of dihydropyridine calcium channel antagonists, angiotensin-converting enzyme inhibitors,

angiotensin receptor blockers, central α-2 agonists, β-adrenergic blockers and renin inhibitors is recommended. Verapamil, hydralazine or α-adrenergic blocker including prazosin/terazosin hydrochloride can be chosen as substitute [26,68]. However, adjustment of antihypertensive therapy is sometimes impractical and may cause severe side effects [69]. Without the replacement, interpretation of ARR is possible as long as renin remains suppressed [70]. Thus, omission of the medical discontinuity has been suggested [71]. Under such circumstances, antihypertensive treatment is only substituted when renin is not suppressed but the ARR and index of suspicion are high after the first screening [71].

The assessment of the ARR is based on the measurement of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) or direct renin concentration (DRC) [26]. The technique of liquid chromatography-tandem mass spectrometry (LC-MS/MS) offers a new option to assess the ARR by measuring PAC and plasma renin concentration. It reached a high accuracy in differentiating patients with PA from those with EH [72,73].

Confirmatory testing

There are four available confirmation tests: oral salt loading test (SLT), SIT, fludrocortisone suppression test (FST), and captopril challenge test (CCT) (summarised in Table 2). Further details are provided in the Endocrine Society Clinical Practice Guideline which recommends diagnosing PA based on ≥ 1 confirmatory tests, while patients with spontaneous hypokalemia and high PAC (> 20 ng/dL or > 550 pmol/L) relative to suppressed renin below detection levels can bypass confirmatory testing [26,68].

SIT and SLT are not applicable in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia or severe hypokalemia due to acute volume overload which may cause cardio-cerebrovascular events [26,74]. Because aldosterone levels increase in the upright

position in nearly all patients with bilateral PA and in up to half of patients with unilateral PA [75], the seated position instead of recumbence during saline infusion is suggested as a more effective approach [75,76]. The cut-off value for seated saline suppression testing (SSST) was determined as 162 pmol/L after comparing results of FST and SSST in 100 patients with PA which attained a higher sensitivity (87%) than that of recumbent saline suppression testing (38%) without compromising specificity (94% vs 94%) [75].

FST is considered as the reference standard when comparing efficacy of confirmation tests due to its high reliability [75,76]. It is nevertheless the most complicated and labour-intensive (up to 5-day hospitalization), and is thus less available than SIT and CCT in hypertension units [77].

The CCT is advantageous in terms of simplicity and absence of risk of fluid overload and hypokalemia, whereas equivocal results have been reported [78]. A study performed comparisons of three tests (SIT, CCT and FST) in 135 patients with PA and 101 patients with EH, and identified that a cut-off of post-CCT PAC (11 ng/dL) resulted in a high diagnostic accuracy (a sensitivity of 90% and specificity of 90%). SIT achieved a similar sensitivity (85%) and specificity (92%) when applying an optimised cut-off of post-SIT PAC (8 ng/dL), thus supporting CCT and SIT to be feasible alternatives to FST [79]. A meta-analysis systematically reviewed 26 articles with 3686 patients showed similar pooled sensitivities of CCT (87%) and SIT (85%) with that of FST (87%) though the pooled specificities were both lower than the reference test (84%, 87% and 95%, respectively) [80].

Subtype differentiation

Once the diagnosis of PA is established, adrenal imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) is mandatory to exclude the rare but highly malignant disease adrenal carcinoma [26]. However, subtype differentiation of unilateral from bilateral PA cannot

solely rely on adrenal imaging because of the low sensitivity for detection of micro-APA <10 mm in diameter [26] and inability to provide functional information. Many studies have reported a low rate of correct subtype differentiation by imaging alone, ranging from 50-80% in patients with confirmed PA [81-84]. Only a restricted subgroup of patients can rely on CT for subtype differentiation [26] and evidence in support of this comes from two studies which achieved an accuracy of 100% in lateralisation among young patients (aged < 35 years) with CT appearance of a large nodule > 10 mm in diameter and normal contralateral adrenal gland, marked PAC (> 30 ng/dL) and spontaneous hypokalemia [84,85].

AVS is endorsed by Endocrine Society guideline to differentiate unilateral from bilateral forms [26]. Prior to AVS, adjustment of antihypertensive medications follows the same principle in ARR screening however some evidence suggests that MR antagonist therapy may be continued during AVS provided that renin values remain low [86,87].

AVS without stimulation of adrenocorticotropic hormone (ACTH) is performed in the early morning after patients have stayed at least 1 h recumbence to avoid confounding posture-induced stimulation of the RAS and increase success rate under a higher stimulation level of the morning ACTH [68,88]. By contrast, in AVS employing ACTH stimulation via either constant cosyntropin infusion (50 μg/h, started 30 min before AVS) or bolus (usually 0.25 mg), the procedure time is more flexible, and a less technical-demanding sequential catheterisation can be performed, as well as avoiding the risk of allergic reaction [89-91]. However, ACTH stimulation is administered in only about 40% of referral units worldwide due to concerns of lowering lateralization [92]. It was reported in a recent study that ACTH loading during AVS irrespective of approach improved the rate of successful cannulation from 67% to 89% and decreased lateralisation indices from 62% to 28%, but did not interfere the clinical and biochemical success in patients with APA [93].

Selectivity index (SI) is calculated as the ratio of cortisol in the adrenal vein and in a peripheral vein and is used to confirm adequate cannulation of adrenal veins. There is no consensus on the standardized cut-off of SI. Most specialised centres adopt SI>2 to 3 in unstimulated AVS, and >3 to 5 in AVS with ACTH stimulation [89,90]. A less stringent cut-off permits higher AVS success rate though it potentially compromises specificity [94]. Instead of altering cut-off of SI, a rapid intra-procedure cortisol assay can promote success rate of catheterisation from 50%-73% to 85-97% [95-98], and its efficacy is currently sought by a randomized prospective study [99]. Lateralisation index (LI) is calculated by aldosterone/cortisol ratio in ipsilateral adrenal venous sample corrected by that ratio in contralateral sample. Likewise, there is a wide variety of LI cut-off value in referral centres [100], and a LI cut-off of 4 was recommended for unstimulated AVS and 2 for ACTH-stimulated AVS [89,90]. In patients with their LI falling into the range of 2-4, some centres employ contralateral ratio (CLR) calculated by aldosterone/cortisol ratio of contralateral adrenal vein corrected by that ratio of peripheral vein as a complement to define co-existing contralateral suppression (cut-off: CLR $\leq$ 1) [68,100]. Metanephrine, produced by the adrenal medulla, circulates at a much higher concentration and is less sensitive to stress than cortisol. Because of these properties, metanephrine is a useful alternative to cortisol for establishing AVS selectivity and performs better than cortisol during procedures without ACTH stimulation [101]. Further, for APAs with co-secretion of cortisol and aldosterone, cortisol may confound the interpretation of AVS results when used for the normalisation of blood dilution in unstimulated procedures and the assessment of lateralisation [102].

D) Future approaches for subtype differentiation

Novel approaches have been investigated in recent years to replace or serve as a conjunction with traditional methods in lateralisation. Positron emission tomography (PET)-CT using radiotracer ^{11}C-metomidate, an inhibitor of 11β-hydroxylase and aldosterone synthase, was demonstrated as a potential non-invasive alternative to AVS [103]. The high specificity and affinity of ^{11}C-

metomidate to CYP11B enzymes permit distinguishing cortical masses from medullary masses, and dexamethasone prior to imaging increased the difference of maximum standardised uptake values between tumour and normal adrenal by 25.6% ($P < 0.01$) which was absent in BAH, thereby differentiating unilateral from bilateral PA [104,105]. A recent study reported that a treatment decision based on ^{11}C-metomidate PET-CT achieved biochemical cure in 2 of 4 patients with PA [106]. Radiotracer ^{68}Ga-Pentixafor binding to chemokine receptor 4, which is overexpressed in APA [107], may serve as another alternative as long as uptake difference between unilateral and bilateral subtypes is proven.

Mutated forms of the potassium channel KCNJ5 drive aldosterone excess in a large proportion of APAs [108]. In a recent development, macrolide antibiotics have been identified which inhibit *KCNJ5* mutants and blunt the expression of CYP11B2 and aldosterone production in *KCNJ5*-mutated adrenocortical and adenoma cells *in vitro* and *ex vivo* [109,110]. A study is now dedicated to assessing the utility of the macrolide antibiotics clarithromycin and roxithromycin during AVS or the diagnostic work-up of PA to identify patients with *KCNJ5*-mutated APAs [111].

LC-MS/MS-based peripheral venous steroid profiling has shown potential utility for the classification of unilateral and bilateral forms of PA [112-114]. The use of LC-MS/MS in this respect is likely associated to the underlying genotype of APAs which can be predicted with 92% accuracy [115].

E) Outcomes of treatment

The potential reversal of adverse effects associated with PA after treatment have been intensively studied. LV hypertrophy can be reversed after surgical or medical management as demonstrated by a regressed rate of LV hypertrophy and LV mass index to levels comparable with optimally treated patients with EH [116]. A lower LV mass index in surgically-treated patients with PA compared

with MR antagonist therapy one year after initiation of treatment (P = 0.024) has been reported [117]. A retrospective cohort study compared cardiovascular outcomes between 602 patients with PA treated with MR antagonists and 41853 age-matched patients with EH at ten-year follow-up and reported an excess incidence of adverse outcomes including atrial fibrillation and mortality limited to patients with sustained suppressed renin activity (<1 μg/L per h) (adjusted hazard ratio [HR] 2.83 [95% CI 2.11–3.80] and 1.79 [1.14–2.80], respectively, vs EH) [118].

Evaluation of atrial fibrillation in 201 surgically-treated and 195 medically-treated patients with PA compared with 40092 age- and blood pressure-matched patients with EH with mean follow-up of 8 years demonstrated a higher risk in medically-treated patients with sustained renin suppression (<1 μg/L per h) (adjusted HR, 2.55 [95% CI, 1.75-3.71]). In contrast, medically-treated patients with elevated renin levels and patients with surgical therapy showed similar risks of atrial fibrillation relative to patients with EH [119]. The incidence of atrial fibrillation has also been prospectively assessed in patients with EH and patients with PA treated surgically or medically after a median of 11.8 years. Both univariate (90.0% vs 97.8%, P=0.002) and multivariate analyses (HR, 1.82 [95% CI, 1.08–3.08]) showed that medically treated patients displayed a lower atrial fibrillation-free survival than patients with EH, whereas a similarity of survival rates was noted in adrenalectomized patients with PA and EH with optimal treatment [120].

A large population cohort study compared (mean follow up, 5.2 years) of 2367 patients with PA with diabetes excluded with 9468 propensity score-matched patients with EH and identified that the risk of newly developed diabetes was attenuated in patients with PA treated with unilateral adrenalectomy (HR 0.60, P < 0.01, vs EH). The decreased incidence of diabetes was also shown in surgically-treated patients with APA (n=596) relative to matched patients with EH (n=3016) (HR 0.61, P < 0.001). In contrast, MR antagonist therapy had no protective effect from diabetes in

patients with PA (including those with APA), and even resulted in an increased risk in patients with PA than those with EH (HR 1.16, P < 0.001) [121].

A study which retrospectively investigated renal parameters in 400 medically treated, 120 surgically treated patients with PA and 15474 age- and glomerular filtration rate-matched patients with EH showed that surgical removal of an APA mitigated the risk of chronic kidney disease to a level comparable to that in patients with EH (HR 0.71 [95% CI 0.39-1.30]). In contrast, the increased risk of chronic kidney disease was maintained in medically-treated patients with PA (HR 1.63 [95% CI 1.33-1.99], vs EH) in whom the adjusted annual glomerular filtration rate continued to decline at a greater level compared with patients with EH (HR −1.6 [95% CI, -1.4 to -1.8] vs −0.9 [95% CI, -0.9 to -1.0]) [122].

An international initiative using the Delphi method established a set of standardised criteria for the assessment of outcomes after surgical management of unilateral PA. The PASO (Primary Aldosteronism Surgical Outcome) study defines six different outcome levels (complete, partial and absent clinical or biochemical success). Clinical success was defined by blood pressure measurements and antihypertensive medication usage, biochemical success was determined by hormonal and biochemical parameters. Application of these criteria to an international cohort of patients determined complete clinical success in 37% and significant clinical benefits in 84% of 705 patients. Partial and absent biochemical success was identified in 6% of 699 patients indicating persistent aldosteronism (or conceivably recurrence) despite successful AVS using stringent LI (ranging from 4.4 to 10) and total unilateral adrenalectomy [123]. Clinical remission (complete clinical success) after surgery can be predicted using a 25-point score developed by the PASO investigators (PASO score) based on 6 presurgical parameters (known duration of hypertension, sex, antihypertensive medication dosage, body mass index, target of organ damage and size of largest nodule at imaging). The use of the score was rendered user-friendly in an online tool (PASO

predictor) which applies an optimal cut-off of 16 points with an area under the curve of 0.839 to predict clinical remission after surgery with 79.2% accuracy (71.3% of sensitivity and 84.4% of specificity) [124]. A downloadable PASO predictor is available at: https://github.com/ABurrello/PASO-Predictor/raw/master/00 - PASO Predictor.xlsm.

F) Summary and perspectives

Powerful approaches for screening, confirmatory testing and lateralisation of aldosterone production have been developed for the diagnosis of PA. Despite this, PA remains underdiagnosed exposing these patients to an increased risk of cardiovascular, metabolic, renal and psychological complications. The screening of all patients with hypertension has been suggested by several experts but the increased burden on health systems warrants a cost-benefit analysis. Innovative approaches which may find an application in the future diagnostic work up of PA include molecular imaging to decrease invasive investigations, mass spectrometry to improve the specificity of the assays and harmonize the reference intervals between laboratories and macrolide antibiotics to characterize primary hyperaldosteronism linked to mutations in APAs. Adrenalectomy reverses the risk of specific complications associated with PA but medical treatment requires close surveillance for effective antagonism of the MR to avoid long-term complications.

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Practice points

- PA is a common endocrine cause of hypertension which can be surgically cured or treated with specific pharmacologic therapy
- PA is underdiagnosed and individuals with untreated (or inappropriately treated) PA have an increased risk of cardiovascular events and target organ damage
- Diagnosis of PA is achieved by a 3-step procedure comprising screening, confirmation testing and subtype differentiation
- Screening is performed by assessment of the ARR in patients with a higher likelihood of PA
- Confirmatory testing is necessary to demonstrate autonomous production of aldosterone
- AVS is recommended to localize the overactive adrenal in patients who wish to pursue surgical treatment
- AVS can be bypassed in patients with a unilateral adrenal mass (>10 mm diam) and a normal appearing contralateral gland with marked aldosterone excess and spontaneous hypokalaemia
- Adrenalectomy for unilateral PA results in cure of hypertension in 37% of patients but significant clinical benefits are achieved in 84%
- Titration of MR antagonist therapy to increase plasma renin levels may be an effective approach to avoid excess cardiovascular risk associated with medically-treated patients

Research agenda

- Screening of all patients with hypertension maybe justified but a cost-benefit analysis is required considering the increased burden to health systems
- Accurate methods to select patients with unilateral PA for adrenalectomy are needed to avoid AVS in medically-treated patients
- Further research should define the utility of novel approaches such as mass spectrometry measurements, functional imaging and macrolide antibiotics in the diagnostic workup of PA

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Table 1: Prevalence of PA in patients with hypertension.

Study	Study type	Center	Screened patients with HTN (N)	Positive screen test (%)	Positive conf. test (%)	Subtype method	APA: BAH (%)	HypoK$^+$ (%)
Gordon et al (1993) [30]	R	PCC	52	11.5	11.5	CT/ AVS	33: 33	0
Loh et al (2000) [34]	P	PCC	350	18	4.6	CT/ AVS	50: 50	37.5
Mosso et al (2003) [35]	R	PCC	609	10.3	6.1	NA	NA	2.7
Omura et al (2004) [36]	P	PCC	1020	11.7	8.1	CT/ AVS	74: 20	24.6
Westerdahl et al (2006) [38]	P	PCC	200	25	8.5	NA	NA	NA
Williams et al (2006) [39]	R	PCC	347	19.6	3.2	NA	NA	Excluded
Fogari et al (2007) [40]	P	PCC	3000	22.8	5.9	CT	30: 63	24.8
Westerdahl et al (2011) [41]	P	PCC	200	18.0	5.5	CT/ AVS	27: 73	NA
Monticone et al (2017) [7]	P	PCC	1672	13.9	5.9	CT/ AVS	27: 65	29.3
Karashima et al (2017) [42]	P	PCC	82	40.2	3.7	NA	NA	NA
Käyser et al (2018) [43]	R	PCC	343	21.6	2.6	NA	NA	NA
Gordon et al (1994) [31]	P	RC	199	10.6	8.5	CT/ AVS	29: 35	Excluded
Brown et al (1996) [125]	P	RC	74	8.1	2.7	NA	NA	Excluded
Lim et al (2000) [126]	R	RC	465	16.6	8.8	NA	NA	4.7
Rossi et al (2002) [127]	P	RC	1046	12.8	6.3	CT	24: 76	NA
Stowasser et al (2003) [128]	P	RC	300	19.7	18.0	CT/ AVS	28: 63	13.0
Strauch et al (2003) [129]	P	RC	402	21.6	19.2	CT/ AVS	36: 42	NA
Nishizaka et al (2005) [130]	P	RC	265	30.2	10.2	NA	NA	40
Douma et al (2008) [131]	R	RC	1616	20.9	11.3	NA	NA	45.6
Ribeiro et al (2009) [132]	R	RC	105	8.6	1.0	NA	NA	NA
Pedrosa et al (2011) [133]	P	RC	125	11.2	5.6	CT	14:86	NA
Rios et al (2011) [134]	P	RC	123	16.3	6.5	CT	25:75	50
Sigurjonsdottir et al (2012) [135]	P	RC	353	13.0	5.7	CT/ AVS	50:20	NA
Sang et al (2013) [136]	P	RC	1656	29.8	7.1	CT/ AVS	33:26	52.5
Galati et al (2016) [47]	P	RC	296	4.7	0.7	NA	NA	0
Gilani et al (2019) [54]	R	RC	80	10.0	10.0	NA	NA	NA

APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; BAH, bilateral hyperplasia; conf., confirmatory; CT, computed tomography; HTN, hypertension; HypoK+, hypokalaemia in patients with confirmed PA; N, number; NA, not available; P, prospective; PA, primary aldosteronism; PCC, primary care center; R, retrospective; RC, referral center.

Table 2: Characteristics of four confirmatory tests.

Confirmatory test	Procedure	Diagnostic cut-off values	Advantage	Disadvantage	Sensitivity	Specificity	Method for increasing accuracy
SIT	0.9% saline infusion (2 L over 4 h)	PAC> 5-10 ng/dL (140-280 pmol/L)	Simple procedure	①Risk of fluid overload and hypokalemia; ②Low sensitivity	73-92% [80]	72-97% [80]	Seated SIT
SLT	6 g sodium chloride per day for 3 days	Urinary Aldo> 12 μg/24h (33 nmol/24h) or >14 μg/24h (39 nmol/24h)	Simple procedure	①Risk of fluid overload and hypokalemia; ②Low patient reliability for urine collection	NA	NA	NA
FST	0.1 mg oral fludrocortisone every 6 h for 4 days	Upright PAC> 6 ng/dL (170 pmol/L) on day 4 at 10:00 with PRA< 1 ng/mL/h and plasma cortisol less than value at 07:00	Most reliable	Most complicated, labor-intensive and costly	NA	NA	NA
CCT	25-50 mg oral captopril	Decrease in PAC≤ 30% (or ARR> 200 pg/mL/ng/mL/h) or Aldo (≥ 8.5 ng/dL or ≥ 240 pM) and ARR≥ 30 ng/dL/ng/mL/h	①Simple procedure; ②No risk of fluid overload and hypokalemia	Possibility of equivocal results	70-100% [80]	68-95% [80]	Application of optimized cut-off of PAC

Aldo, aldosterone; ARR, aldosterone-to-renin ratio; CCT, captopril challenge test; FST, fludrocortisone suppression test; NA, not available; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SIT, saline infusion test; SLT, oral salt loading test.