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Review Article

The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism

Gian Paolo Rossi [a,*], Valeria Bisogni [a], Alessandra Violet Bacca [b], Anna Belfiore [c], Maurizio Cesari [a], Antonio Concistrè [d], Rita Del Pinto [e], Bruno Fabris [f], Francesco Fallo [g], Cristiano Fava [h], Claudio Ferri [e], Gilberta Giacchetti [i], Guido Grassi [j], Claudio Letizia [d], Mauro Maccario [k], Francesca Mallamaci [l], Giuseppe Maiolino [a], Dario Manfellotto [m], Pietro Minuz [h], Silvia Monticone [n], Alberto Morganti [o], Maria Lorenza Muiesan [p], Paolo Mulatero [n], Aurelio Negro [q], Gianfranco Parati [r], Martino F. Pengo [r], Luigi Petramala [d], Francesca Pizzolo [h], Damiano Rizzoni [p], Giacomo Rossitto [a,s], Franco Veglio [n], Teresa Maria Seccia [a]

[a] Clinica dell'Ipertensione Arteriosa, Department of Medicine - DIMED, University of Padua, Italy
[b] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[c] Clinica Medica "A. Murri", Department of Biomedical Sciences and Human Oncology, University of Bari Medical School, Bari, Italy
[d] Department of Translational and Precision Medicine, Unit of Secondary Arterial Hypertension, "Sapienza" University of Rome, Italy
[e] University of L'Aquila, Department of Life, Health and Environmental Sciences, San Salvatore Hospital, L'Aquila, Italy
[f] Department of Medical Sciences, Università degli Studi di Trieste, Cattinara Teaching Hospital, Trieste, Italy
[g] Department of Medicine, DIMED, Internal Medicine 3, University of Padua, Italy
[h] Department of Medicine, University of Verona, Policlinico "G.B. Rossi", Italy
[i] Division of Endocrinology, Polytechnic University of Marche, Ancona, Italy
[j] University of Milano-Bicocca, Italy
[k] Endocrinology, Diabetology, and Metabolism, Department of Medical Sciences, University of Turin, Turin, Italy
[l] CNR-IFC Clinical Epidemiology of Renal Diseases and Hypertension, Reggio Calabria, Italy
[m] UO Medicina Interna, Ospedale Fatebenefratelli Isola Tiberina, Rome, Italy
[n] Hypertension Unit, Division of Internal Medicine, Department of Medical Sciences, University of Turin, Italy
[o] Centro Fisiologia Clinica e Ipertensione, Ospedale Policlinico, Università Milano, Milan, Italy
[p] Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, Italy
[q] Department of Medicine, Center for Hypertension, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy
[r] Department of Medicine and Surgery, University of Milano-Bicocca and Istituto Auxologico Italiano, IRCCS, Milan, Italy
[s] University of Glasgow, Institute of Cardiovascular and Medical Sciences, Glasgow, UK

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ABSTRACT

Background and aim: Considering the amount of novel knowledge generated in the last five years, a team of experienced hypertensionlogists was assembled to furnish updated clinical practice guidelines for the management of primary aldosteronism.

Methods: To identify the most relevant studies, the authors utilized a systematic literature review in international databases by applying the PICO strategy, and then they were required to make use of only those meeting predefined quality criteria. For studies of diagnostic tests, only those that fulfilled the Standards for Reporting of Diagnostic Accuracy recommendations were considered.

Results: Each section was jointly prepared by at least two co-authors, who provided Class of Recommendation and Level of Evidence following the American Heart Association methodology. The guidelines were sponsored by the Italian Society of Arterial Hypertension and underwent two rounds of revision, eventually reexamined by an External Committee. They were presented and thoroughly discussed in two face-to-face meetings with all co-authors and then presented on occasion of the 36th Italian Society of Arterial Hypertension meeting in order

* Corresponding author. DIMED –Clinica dell'Ipertensione Arteriosa, University Hospital, via Giustiniani, 2; 35126, Padova, Italy.
E-mail address: gianpaolo.rossi@unipd.it (G.P. Rossi).

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to gather further feedbacks by all members. The text amended according to these feedbacks was subjected to a further peer review.

Conclusions: After this process, substantial updated information was generated, which could simplify the diagnosis of primary aldosteronism and assist practicing physicians in optimizing treatment and follow-up of patients with one of the most common curable causes of arterial hypertension.

1. Introduction

Primary aldosteronism (PA) is the most common, but probably the least identified cause of endocrine arterial hypertension. This is partly because of the diffuse misconception that it is extremely rare and partly because hypokalemia, one of its clinical hallmarks, nowadays often lacks. Therefore, many PA patients are mislabeled as being affected by primary (essential) hypertension because they are never screened for PA. Accordingly, they remain exposed lifelong to the detrimental effects of hyperaldosteronism.

After publication of the last guidelines [1,2], many important publications have appeared in this field, which can justify changes of practice in the clinical management of PA. Hence, we have assigned the task to prepare updated guidelines for the screening, subtyping,

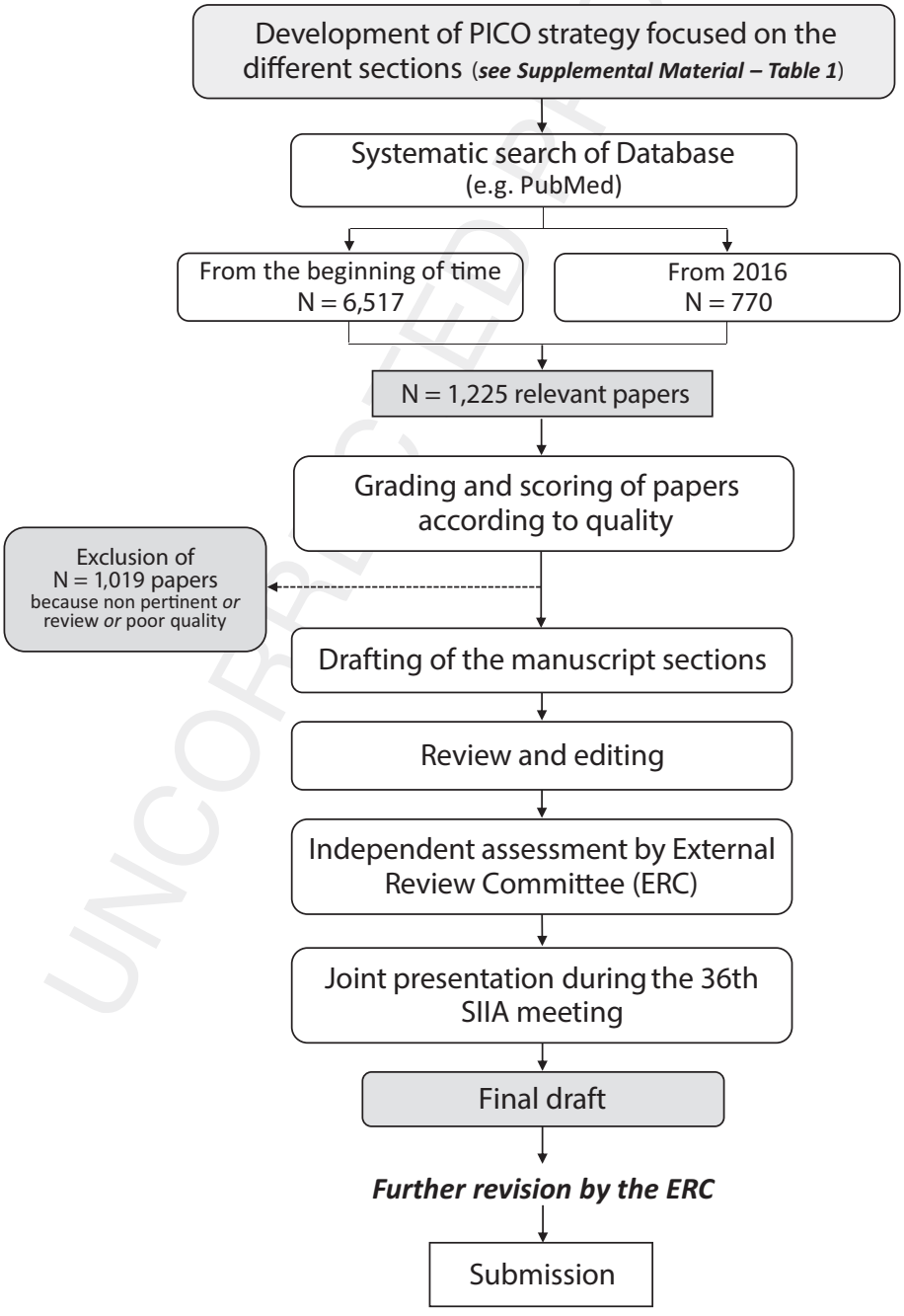

Fig. 1. Main steps followed in the preparation of the Guidelines.

and treatment of PA to a panel of renowned hypertensionlogists (Fig. 1).

To this aim, they were asked to follow the overall methodology described in detail in the Supplemental Material, which is summarized here. After identification of relevant publications in the literature with the PICO strategy [3] (Table 1 of Supplemental Material), they were requested to grade and select only high-quality papers as a basis for advice/recommendation (Fig. 1) and to grade their suggestions by Class of Recommendation and Level of Evidence following an internationally accepted methodology (Table 2 of Supplemental Material) [4].

These guidelines also adopted an unprecedented strategy for the evaluation of accuracy of diagnostic tests: they considered only studies that fulfilled the STARD recommendations, which require a gold standard as reference (Figs. 1 and 2 of Supplemental Material) [5]. This was judged to be necessary for PA, because a continuum exists between this condition and low-renin essential hypertension [6], which means that many hypertensive patients with only borderline elevated, or even normal plasma aldosterone concentration (PAC) have a high aldosterone-renin-ratio (ARR) owing to low-renin and cannot be attributed with certainty to one group or the other. Hence, when assessing accuracy of diagnostic tests the only useable "gold reference" for PA, i.e. the subtypes that can be unambiguously diagnosed, entail the unilateral forms, i.e. aldosterone-producing adenoma (APA) and unilateral hyperplasia (UAH), which can be defined conclusively based on pathology, and follow-up examination [7], and the familial forms for which genetic tests exist.

2. Definition and prevalence of primary aldosteronism

PA is a heterogeneous group of familial and sporadic disorders characterized by hypertension secondary to overproduction of aldosterone that seems autonomous from renin. Sporadic PA are the most common forms and are caused by APA, UAH, or bilateral adrenal hyperplasia (BAH) [8]. The latter is usually held to prevail; however, when adrenal vein sampling (AVS) was systematically used the unilateral forms entailed two thirds of the cases, suggesting that AVS is key for proper identification of the underlying pathology [9]. Familial Hyperaldosteronism (FH) is relatively uncommon: to date four forms of FH due to different germ-line mutations [10] have been identified (see later) [8,11,12].

The prevalence rate of PA varies according to the population examined and the criteria used to diagnose it: in general practice it can range from 5.9%, when a complete diagnostic work-up was performed [13], up to 34% when only the aldosterone-renin ratio (ARR) was taken as a surrogate for the diagnosis [14]. In hypertensives referred to specialized centers PA was found to involve 11.2% of the patients [9], albeit it increases along with the severity of high blood pressure (BP) elevation, from 3.9% to 9.7%, and up to 11.8% in hypertension stage 1, 2, and 3, respectively [13], and up to 20% in patients with drug-resistant hypertension **(Level of Evidence B)** [15]. PA was also reported to involve about 2–3% of patients with an asymptomatic incidentally discovered adrenal mass [16].

Although hypokalemia (<3.5 mEq/L), either spontaneous or diuretic-induced, was traditionally held to be the presentation sign of PA, nowadays it occurs only in a minority (9–37%) of PA patients [9,17], nonetheless, when present and not due to obvious causes, such as vomiting or diarrhea, it is a strong clue to the presence of PA.

Notwithstanding the evidences for a high prevalence, PA is still regarded as very rare: in a retrospective survey of general practitioners in Germany and Italy only 1–2% of their hypertensive patients were screened [18]. On the whole, these findings call for actions to increase knowledge of the high prevalence of PA, and implementation of broader strategies for screening and subtyping based on simplified algorithms.

Highlights	Class of Recommendation	Level of Evidence
• PA entails a heterogeneous group of common sporadic forms and rarer familial forms.	**I**	**A**
• Its prevalence varies according to the cohort of hypertensive patients studied, on the whole between 5.9% and 20%.	**I**	**B**
• Familial forms are rare and mostly characterized by autosomal dominant transmission.	**I**	**A**
• Sporadic forms comprise surgically curable unilateral causes (aldosterone-producing adenoma and unilateral hyperplasia) and medically treatable bilateral adrenal hyperplasia.	**I**	**A**
• Despite the high prevalence of PA only 1–2% of hypertensive patients are screened for it.	**II**	**B**

3. Case detection

3.1. When and how to perform the screening

Table 1 summarizes the conditions in which the diagnostic work-up for PA is recommended (**Class of Recommendation II, Level of Evidence B**). An observational study, however, suggested that PA can follow

Table 1
Categories of patients where the screening for primary aldosteronism is recommended.

Condition	Description
Severe hypertension	Hypertension stage 3, i.e. systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg
Resistant hypertension	Blood pressure values that remain above goal in spite of concurrent use of three antihypertensive agents of different classes. If tolerated, one of the three agents should be a diuretic, and all agents should be prescribed at maximum recommended (or maximally tolerated) antihypertensive doses.
Patients with hypertension associated with (permanent or intermittent) spontaneous or diuretic-induced hypokalemia	Serum potassium (K^+) < 3.5 mmoL/l in absence of other potential causes of hypokalemia (i.e. gastrointestinal disorders, abuse of licorice, etc.).
Hypertension or hypokalemia associated with adrenal incidentaloma	Hypertensive patients with an adrenal mass detected on imaging.
Normal potassium levels (≥3.5 to ≤ 5.0 mmoL/l) associated with another of the above-mentioned indications for PA screening	
When hypertension-mediated organ damage and cardiovascular or renal morbidity are more severe than expected from the level and duration of hypertension	Hypertension-mediated organ damage such as microalbuminuria, renal disease, hypertensive retinopathy, left ventricular hypertrophy and diastolic dysfunction, etc.
Hypertension and sleep apnea	See 'Comorbidities' section for further explanations.
Hypertension and atrial fibrillation	See 'Comorbidities' section for further explanations.
Hypertension and a family history of early onset hypertension and/or cerebrovascular accident at a young age (<40 years) and of first-degree relatives with primary aldosteronism	See 'Testing for familial forms of primary aldosteronism and detection of genetic mutations' for further explanations.
Newly-presenting patients with hypertension and a high chance of cure with adrenalectomy, as, for example, young, women, with a short duration of hypertension	

a long natural history starting with renin suppression and normotension, progressing into florid disease, and ultimately evolving in stage 2–3 and/or drug-resistant hypertension [19]. Along with the documented feasibility of preventing cardiovascular complications with an early diagnosis followed by a targeted treatment [20,21], this would justify wider screening strategies.

Hypokalemia, when not attributable to obvious causes, is a strong clue, but normokalemia does not allow to exclude PA [22]. As mentioned, hypokalemia is rare nowadays in patients with PA [9,17], and, therefore, plasma potassium measurement is both insensitive and not specific for the screening of PA. A 24-h urinary potassium excretion exceeding what expected from serum potassium levels, for example >30 mEq/24-h in a patient with serum potassium below 3.5 mEq/L, indicates exposure of the renal tubule to aldosterone excess, particularly if the patient's natriuresis is below 200–300 mEq/day, as increased distal tubular delivery of sodium increases kaliuresis. The measurement of potassium and sodium in a 24-h urine collection is, therefore, recommended for a proper interpretation of ARR and for corroborating a diagnosis of PA **(Class of Recommendation II, Level of Evidence B)**.

The diagnosis of PA requires demonstration of low or undetectable renin levels and plasma aldosterone concentration (PAC) that is inappropriately high for salt and volume status. However, when interpreting the PAC values four main facts should be considered: (i) the documented existence of cases of normo-aldosteronemic PA, where the only clue of PA is low renin; (ii) the fact that borderline high PAC levels can denote PA if Na^+ intake exceeds 200 mEq/day (about 11 gr per day of NaCl); (iii) the interindividual sensitivity to aldosterone, for example, the higher sensitivity of patients of African-American ancestry [23]; (iv) the well-known pulsatility of aldosterone secretion, meaning that even in patients with PA PAC can occasionally be in the normal range when it is at its nadir. Hence, high PAC levels (exceeding a given cut-off, for example 15 ng/dL or 416 pmoL/l) are by no means a *conditio* sine *qua non* for diagnosing PA and attention should be paid to renin levels that, if low, are a strong clue to the presence of a volume-dependent form of hypertension of which PA is the paradigm.

In 1981 to simplify the case detection of PA Hiramatsu et al. introduced the ARR [24]; its superiority over the isolated measurement of PAC, plasma renin activity (PRA) or direct renin concentration (DRC) has been thereafter convincingly demonstrated [9,22,25]. Considering its high sensitivity and accuracy in identification of PA, and also its within-patient reproducibility when performed under standardized conditions [26], we recommend using this test for the initial evaluation of the hypertensive patients falling into the categories enlisted in Table 1 **(Class of Recommendation I, Level of Evidence B)**.

The direct measurement of renin concentration (DRC) based on chemiluminescence has broadly replaced the PRA assay because of its advantages, including the handling of blood samples at room temperature, precision in the low range levels of renin, lower cost, lack of radioactivity, and also because it is fast and lends itself automation, thus shortening the time from blood sampling to test results **(Class of Recommendation II, Level of Evidence B)** [27]. If the ARR measurement is not available, the patient must be referred to a center that can perform this test in a standardized reproducible manner.

Highlights	Class of Recommendation	Level of Evidence
• Some specific conditions should alert for PA, such as severe and/or resistant hypertension.	**II**	**B**
• The diagnosis of PA requires demonstration of low or undetectable renin levels and PAC that are inappropriate by high for salt and volume status.	**II**	**A**
	II	**A**

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Highlights	Class of Recommendation	Level of Evidence
• The measurement of DRC is a valuable alternative to PRA for assessing low renin in PA patients.		
• PAC values are pulsatile. They can occasionally be only borderline elevated in PA, particularly in patients of African ancestry an in the elderly.	**I**	**B**
• The measurement of serum Na^+ and K^+ and in 24-h urine is fundamental for a proper interpretation of the PAC, renin and ARR values.	**II**	**B**

3.2. Technical aspects

When measuring the ARR, standardization of the sampling conditions and careful consideration to potential confounders (listed in Table 2) are recommended for a proper interpretation of the ARR results **(Class of Recommendation II, Level of Evidence A)**.

Since renin and aldosterone levels show a circadian rhythm, being highest at awakening in the morning **(Class of Recommendation II, Level of Evidence A)** [28], the time of blood sampling should be standardized and taken into consideration when interpreting results. Posture also influences renin and PAC: standing up raises renin, and, thereby, PAC. To allow assessment of baseline hormonal values we recommend to obtain the blood samples after 60 min of quiet supine or sitting rest **(Class of Recommendation II, Level of Evidence B)**, the conditions that provided optimal results in the PAPY Study [9].

Table 2
Drugs and conditions that affect aldosterone, renin, and aldosterone-renin ratio.

Factor	Effect on PAC levels	Effect on renin levels	Effect on ARR
Serum potassium status			
Hypokalemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑
Dietary sodium			
Sodium restriction	↑	↑↑	↓ (FN)
Sodium loading	↓	↓↓	↑ (FP)
Drugs			
β-Adrenergic blockers	↓	↓↓	↑ (FP)
Calcium channel blockers (DHPs)	→↓	↑	↓ (FN)
ACE inhibitors	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
K^+-sparing diuretics	↑	↑↑	↓ (FN)
K^+-wasting diuretics	→↑	↑↑	↓ (FN)
Clonidine			
α-methyldopa	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
Steroids	↓	→↓	↑ (FP)
Contraceptive agents (drosperinone)	↑	↑	↑ (FP)
Clinical conditions			
Old age	↓	↓↓	↑ (FP)
CKD	→	↓	↑ (FP)
Pregnancy	↑	↑↑	↓ (FN)
Renovascular HT	↑	↑↑	↓ (FN)
Malignant HT	↑	↑↑	↓ (FN)

PAC, plasma aldosterone concentration; ARR, aldosterone-renin-ratio; DHPs, dihydropyridines; ACE, angiotensin-converting enzyme; ARBs, angiotensin II type 1 receptor blockers; K^+, potassium; NSAIDs, non-steroidal anti-inflammatory drugs; FP, HT, hypertension; false positive; FN, false negative.
Adapted from J. W. Funder et al.*: The management of Primary Aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 101(5):1889–1916* [1]

The phase of the menstrual cycle should also be considered in women as during the luteal phase false positive ARR results can occur [29].

Blood should be collected slowly to avoid hemolysis, with ensuing "factitious" normokalemia and, if the DRC assay is used, must be kept at room temperature during transportation to the laboratory.

Marked hypokalemia, i.e. < 3.0 mEq/L should be identified and corrected before testing because it lowers PAC [30]. Premenopausal women tested during the luteal phase of the menses and post-menopausal women receiving hormonal replacement therapy can show false positive ARR results due to a more marked rise of PAC than renin [31,32].

3.3. Preparation of the patient

Commonly used substances, such as non-steroidal anti-inflammatory drugs, steroids, estrogen-containing medications, licorice, dopaminergic and antihistaminergic medications, selective serotonin reuptake inhibitor antidepressants, affect aldosterone and/or renin levels and should be withdrawn [33,34]. Likewise, several antihypertensive drugs alter the ARR; diuretics stimulate renin more than aldosterone secretion, thus causing a falsely negative ARR values. ACE inhibitors and angiotensin II receptor blockers (ARBs) raise renin and lower PAC, and, therefore, lower the ARR, while beta-blockers blunt renin and thus raise the ARR (Table 2) [35,36]. Hence, diuretics, ACE inhibitors, ARBs, and beta-blockers, must be stopped before sample collection. In our experience renin can be falsely high with ACEI and ARBs, and falsely low with beta-blockers, even three weeks after stopping these drugs. Hence, we recommend withdrawal of these agents for at least four weeks **(Class of Recommendation II, Level of Evidence C)**.

Yet, withdrawal of all antihypertensive drugs is not recommended **(Class of Recommendation III, Level of Evidence C)** as this can expose patients to the risk of uncontrolled high BP values and/or hypokalemia. The long-acting dihydropyridines calcium channel blockers, doxazosin and/or moxonidine can allow to control of hypertension for 4–6 weeks before measuring the ARR because these drugs minimally affect renin and PAC. Theoretically, verapamil could lower PAC because in vitro it blunts p-glycoprotein, which pumps aldosterone out of the aldosterone-producing cells [37]; in practice, however, widespread clinical experience has shown that verapamil slow release and diltiazem do not decrease the sensitivity of the screening for PA. Thus, they are valuable options, particularly in patients who do not tolerate the dihydropyridines calcium channel blockers. However, in patients with marked hypokalemia, who already have a long PQ interval, these agents may precipitate an atrio-ventricular block. Hence, we recommend achievement of normokalemia with KCl supplementation using 24-h urine potassium excretion as a guide to the number of KCl pills to prescribe, before administering these calcium channel blockers **(Class of Recommendation II, Level of Evidence B)** [38].

Mineralocorticoid receptor antagonists (MRAs) are the most effective agents to control BP and hypokalemia in PA patients [39], particularly in those with resistant hypertension [40]. MRAs withdrawal can put these patients at risk of uncontrolled hypertension and/or severe hypokalemia. The diagnosis can be made in patients on MRAs if PAC is high and renin low [41,42]. A recently completed study suggests that MRAs can be used in the systematic screening of PA [43]. Therefore, if antihypertensive treatment cannot be switched to non-interfering drugs and the patients need additional agents [44], knowledge of the effects of different classes of drugs on the ARR can assist in making the diagnosis **(Class of Recommendation II, Level of Evidence B)** (Table 2) [15,39,40].

Highlights	Class of Recommendation	Level of Evidence
• Currently hypokalemia is absent in the majority of PA patients and, therefore, cannot be used as a screening test.	**II**	**B**
	III	**C**

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Highlights	Class of Recommendation	Level of Evidence
• Withdrawal of all antihypertensive medications is not recommended for measurement of the ARR.		
• Patients should be worked-up for PA under proper conditions (i.e. normokalemia and switching to none interfering treatment).	**II**	**A**
• In patients with marked hypokalemia and/or drug-resistant hypertension MRAs can be administered during screening.	**II**	**B**
• The finding of high PAC and low renin while on drugs expected to rise renin and lower PAC, can allow the diagnosis of PA.	**II**	**B**
• The clinical use of ARR requires careful considerations to the actual values of PAC and renin, and to the factors that can influence these values.	**II**	**B**

3.4. Interpretation of ARR

It is common practice to categorize the ARR results as positive or negative, which is a simplification overlooking the important quantitative information that the ARR provides. In a prospective study of two very large datasets of consecutive hypertensive patients increasingly high ARR values were associated with an exponentially increasing specificity [45], thus indicating that in the clinical decision making the quantitative information provided by the ARR should be taken into account **(Class of Recommendation II, Level of Evidence B)**. This would furnish a high diagnostic accuracy for identification of the surgically curable subtype of PA, thus allowing to directly refer for AVS the patients seeking for surgical cure upon finding a high ARR (e.g. > 50 ng/mUI for PAC/DRC, i.e. 38 ng/dl/ng/ml/h) in line with the suggestion of skipping the confirmatory tests [1].

In clinical practice, one commonly encountered difficulty relates to the different units of measure for renin and PAC furnished by different laboratories, which impact on the ARR value and the ensuing clinical decision making. To address this issue, an ARR App for use in iOS and Androids has been developed to allow calculation of the ARR in different units of measure [46], and is freely downloadable.

Highlights	Class of Recommendation	Level of Evidence
• The ARR is the most popular screening test.	**II**	**B**
• The ARR provides quantitative information that should not be neglected by categorizing its results simply as positive or negative.	**II**	**B**
• A freely downloadable App allows calculation of the ARR in the units provided by the various laboratories.	**II**	**B**

3.5. Renin and aldosterone assays

Plasma renin can be assessed as activity (PRA, ng/ml/h) by measuring angiotensin I generated over time, or with a direct assay that quantifies mass, e.g. active renin (DRC, mIU/L or pg/mL). Head-to-head studies comparing PRA with DRC have shown that with either assay the ARR performed similarly well for screening patients with PA in spite of their having low levels of renin **(Class of Recommendation I, Level of Evidence B)** [47–49]. However, since all available methods loose precision when measuring very low renin values, when calculating the ARR it is common practice to set the low detection limit way at 0.2 ng/mL/h for PRA, or 2 mIU/L for DRC. This avoids false positive results and is

particularly important in patients with low-renin essential hypertension, for example in those who are elderly and/or of African ancestry.

PAC (ng/dL or pmol/L) is usually measured with RIA, which furnished PAC values that varied widely across laboratories, likely depending on plasma extraction and cross reactivity of aldosterone antibodies [50]. Mass spectrometry substantially increases the analytical accuracy of PAC measurements, but this technique is not widely available [51,52].

A major development in this field have been automated chemiluminescent assays, which allow a rapid and accurate simultaneous measure of both DRC and PAC on only 200 μL of plasma with a high within-assay reproducibility (concordance correlation coefficient was 0.92 and 0.93 for renin and PAC, respectively) and very limited manpower [27].

Highlights	Class of Recommendation	Level of Evidence
• Plasma renin can be measured indirectly as angiotensin I generated with the enzymatic assay as PRA or with a direct assay that quantifies active renin (DRC).	**I**	**B**
• With either methods the ARR values are comparable, if correctly calculated, even in the low range.	**I**	**B**
• Automated chemiluminescent assays allow an accurate simultaneous measure of both DRC and PAC with a high within-assay reproducibility and very limited manpower.	**I**	**B**
• To avoid overinflating the values when calculating the ARR it is common practice to set the low detection limit or renin at 0.2 ng/mL/h (for PRA) or 2 mIU/L (for DRC).	**II**	**B**

3.6. *Primary aldosteronism and pregnancy*

Although hypertensive disorders affect 6–8% of all pregnant women [53], to date only 41 PA patients with pregnancies (excluding familial forms) have been reported [54], likely reflecting the difficulty of diagnosing PA during pregnancy [54,55]. Pregnancy is a hyperreninemic hyperaldosteronism state [55,56], because progesterone acts as a potent MRA and, therefore, raises renin and even more markedly PAC (3–10 fold) [57]. Moreover, renin is produced in the uterus and resistance to the vasopressor effect of angiotensin II can further increase renin synthesis in the kidney.

Hypokalemia and/or severe hypertension, especially before week 20, should raise suspicion of PA, which is confirmed if renin is low and ARR is high. Confirmatory tests (see later) are not recommended: saline infusion test should be avoided because pregnant women are volume-expanded and captopril is contraindicated in pregnancy **(Class of Recommendation III, Level of Evidence C)** [54–56].

Magnetic resonance imaging (MRI) is the only imaging test feasible during pregnancy **(Class of Recommendation I, Level of Evidence B)** [55], while computed tomography (CT) scan and AVS involve X-rays exposure and thus are contraindicated **(Class of Recommendation III C)** [54].

In women already diagnosed with an APA adrenalectomy should be performed before undertaking pregnancy. In pregnant women with PA, MRAs should be stopped and replaced by methyldopa, long-acting calcium channel antagonists, or beta-blockers [54,56]. MRAs may be considered only **(Class of Recommendation IIb)** when BP is not controlled with treatment; however, spironolactone and potassium canrenoate have anti-androgenic activity and cross the placenta; therefore, their minimally effective dose should be used. Eplerenone has less anti-androgenic effects and may be considered in the first trimester, when sex differentiation occurs **(Class of Recommendation IIa)** [54–56,58]. Laparoscopic adrenalectomy may be considered during the second trimester in women with APA and uncontrollable PA **(Class of Recommendation IIa, Level of Evidence C)** [54–56,58].

Highlights	Class of Recommendation	Level of Evidence
• Hypokalemia and/or severe hypertension during pregnancy, especially before week 20, should raise suspicion of PA.	**I**	**B**
• Diagnosis is based on high ARR values and can be confirmed by testing for FH or by MRI.	**I**	**B**
• If the diagnosis of APA is already known surgery is recommended before starting pregnancy.	**IIb**	**B**
• When BP is not controlled with treatment, laparoscopic adrenalectomy is preferred in APA patients during the second trimester and MRAs might be added if hypertension is uncontrolled.	**IIa**	**C**

4. Case confirmation

The confirmatory tests are based on the premise that in PA aldosterone secretion is unresponsive to maneuvers that perturbate renin production [59–61]. These tests are justified by the need of avoiding invasive downstream work-up of PA, including AVS [62]. However, they can identify the PA cases that do not suppress aldosterone secretion in response to an acute exposure to salt and volume expansion or to blunting angiotensin II formation [63]. This means that they lead to exclude from further work-up a non-negligible proportion of the PA patients who do suppress PAC [64].

Currently performed confirmatory tests comprise the oral sodium loading test, the saline infusion test, the captopril challenge test, and the fludrocortisone + salt loading test. They are a controversial issue because they are supported by studies that did not fulfil the STARD recommendations [65] requiring validation against a gold reference standard, e.g. a conclusive diagnosis of APA (see Supplemental Material – Fig. 1) [66].

In 2016 the Endocrine Society Guidelines experts, recognizing the burden carried by the confirmatory tests, suggested the possibility of bypassing confirmatory tests in patients with a florid clinical phenotype, e.g. a positive ARR, high PAC (>20 ng/dL) and spontaneous hypokalemia [1]. In 2017 a large study that strictly followed the STARD recommendations provided compelling evidence in support of this recommendation: in two cohorts of consecutive patients showed that the baseline ARR value furnished no less diagnostic accuracy than the either PAC or the ARR values after a captopril challenge, indicating that this confirmatory test provided no diagnostic gain [45]. Consensus is therefore building up that quantitative information conveyed by the ARR [45] could be used to determine if the patient should undergo the downstream work-up or not **(Class of Recommendation IIb, Level of Evidence B)**. Nonetheless, further large prospective studies using the STARD criteria are needed.

Highlights	Class of Recommendation	Level of Evidence
• Confirmatory tests have not been validated following the STARD criteria.	**IIa**	**C**
• They serve as exclusion test, i.e. captopril challenge test, oral sodium loading test, the saline infusion test to avoid subtyping in ARR false positive results, which should be raise if the ARR is properly performed.	**IIa**	**B**
• The confirmatory tests are not necessary in patients with florid phenotype (high ARR, high aldosterone with or without low potassium levels).	**IIa**	**A**

5. Subtyping

5.1. Imaging

Currently an imaging test, preferably CT, is recommended in all PA patients [1] to rule out the presence of an aldosterone-producing carcinoma, and to identify adrenal venous drainage, thus offering a guide to the interventionist performing AVS **(Class of Recommendation IIa, Level of Evidence B)**. However, a CT-based strategy furnished concordant results in only about half of the cases when cosyntropin-stimulated AVS was used as reference golden standard. Moreover, AVS showed unilateral disease in 22% of the CT-negative cases, while CT detected a unilateral mass in 25% of the cases with bilateral or contralateral disease at AVS [67]. Thus, by relying only on CT scan, about one fifth of the patients would have been denied curative adrenalectomy, and a quarter would have undergone unnecessary or inappropriate adrenalectomy [68–71]. These results were recently confirmed in a Japanese study where imaging identified unilateral PA in less than half of the cases only a minority showed concordant results between CT and AVS [72].

Collectively, the available findings on current adrenal imaging techniques support the following conclusions: i) the identification of adrenal micro-adenomas is its main limitation; ii) both CT and magnetic resonance imaging have a poor accuracy in predicting unilateral disease; iii) adrenal imaging it is insufficient for the clinical decision making, e.g. to refer the patients to surgery.

Highlights	Class of Recommendation	Level of Evidence
• All patients with PA require imaging, preferably CT scan.	**IIa**	**B**
• Imaging should be ordered to exclude an aldosterone-producing carcinoma and to identify adrenal venous drainage, thus offering a guide to the interventionist performing AVS.	**IIa**	**B**
• Imaging is not adequate to refer patients for surgery as it does not provide an accurate identification of the culprit adrenal.	**IIa**	**B**

5.2. Adrenal vein sampling

Although being expensive, technically demanding, and carrying a 0.7% risk of adrenal vein rupture, AVS is the key test to identify candidate for unilateral adrenalectomy [73]. As an indication for adrenalectomy, it should be proposed only to patients who have: a) unequivocal biochemical evidence of PA; b) wish to achieve long-term cure of PA with adrenalectomy; c) are reasonable candidates for general anesthesia and surgery; d) do not have any surgically-incurable forms of mineralocorticoid excess **(Class of Recommendation I, Level of Evidence B)** [1, 74].

Data gathered on >2500 AVS studies performed in centers scattered across Europe, Asia, and North America in the Adrenal Vein sampling International Study, showed that of the PA patients with these features only about 70% were offered AVS [74], indicating a low adherence to the guidelines recommendations, in spite of the low (0.7%) rate of major complications [1].

As performance and interpretation of AVS require considerable experience, this test should only be done in tertiary referral centers **(Class of Recommendation II, Level of Evidence B)** [67,68] following correct preparation of the patients. First, to minimize the chance of false results, AVS should be undertaken after switching to non-interfering treatment as described above for case detection (Table 2). Second, hypokalemia, if present, should be corrected before AVS, as it can mask unilateral PA by reducing aldosterone secretion. Third, standardized protocols should be systematically exploited. AVS can be performed with bilaterally simultaneous or sequential catheterization, with or without cosyntropin stimulation. Arguments exist in favor of each technique: simultaneous cannulation avoids stress-induced potential factitious differences generated by fluctuation of adrenal steroids secretion between sides. However, the concordance between two simultaneous AVS was not better than between a simultaneous and a sequential AVS in one study [75], and in the Adrenal Vein Sampling International Study-2 (AVIS-2), the largest registry of PA patients submitted to AVS in four continents [76], several referral centers still used the sequential technique [77]. Therefore, the preferred technique is left to center preference and experience.

AVS can also be performed under unstimulated conditions or during cosyntropin (synthetic adrenocorticotropic hormone, ACTH) stimulation [78,79]. Cosyntropin has two advantages: i) facilitate the ascertainment of selectivity, thus increasing the apparent success rate of cannulation of the adrenal veins; ii) reduce pulsatility of adrenocortical steroid production. It should be preferentially used in centers that have a low success rate in achieving selective cannulation, as recently discussed in-depth **(Class of Recommendation II, Level of Evidence B)** [80]. However, cosyntropin exerts heterogeneous responses in different patients, thus reducing or increasing the lateralization index [81,82], and leading to different results between unstimulated and cosyntropin-stimulated AVS in about 25% of the patients even in a highly experienced center [81]. In a large international registry this led to deny adrenalectomy to surgically curable PA patients [77], or to non AVS-guided adrenalectomy with ensuing worse clinical outcome [76].

The measurement of plasma cortisol concentration (PCC) in adrenal vein and peripheral or inferior vena cava blood samples is used for calculating the selectivity index, and thus to confirm catheter's placement during sampling. It also serves for calculating the lateralization [83,84], as it allows correction for dilution of blood from extra-adrenal sources (see later). This can provide an accurate diagnosis when AVS was bilaterally successful. Metanephrine or androstenedione measurement [85, 86] are valuable alternatives to cortisol in establishing success of AVS and should be used in cortisol-cosecreting APA [87]; which one is better remains to be determined.

The major challenge when performing AVS is the difficulty of catheterizing the right adrenal vein, which is short and shares a common egress with inferior accessory hepatic veins in about 15% of the cases [84]. Lower PCC and PAC in adrenal vein samples than in peripheral samples identify blood sampling in accessors hepatic veins. The intra-procedural rapid cortisol assay during AVS [88], C-arm CT [89], or super-selective catheterization of the right adrenal vein after identification of the hepatic veins by CT [80], can bypass this problem, but unfortunately, C-arm CT is not widely available; moreover, super-selective catheterization is currently feasible only in few Japanese centers [90].

A randomized trial (SPARTACUS) comparing two treatment strategies, one based on cosyntropin-stimulated AVS and one based on CT only [91], failed to detect significant differences in the intensity of antihypertensive medication needed reach the target BP (in defined daily dose - DDD) and the physical or mental scores, assessed as primary endpoints at one year. This led the authors to contend that the extra costs of AVS were unjustified. Unfortunately, these conclusions were not supported by the actual data, because of the many limitations of this trial including the lack of power and the poor performance of AVS [92].

When AVS-guided, adrenalectomy provided biochemical cure in 98%–100% of the cases [93], resolution of hypertension in 42%, with additional 46% showing marked improvement in BP control [21]. Resolution of drug-resistant hypertension was also recently documented in a single-center study and in the AVIS-2 Study [76]. Moreover, AVS-guided adrenalectomy induced regression of LV hypertrophy through an inward type of LV reverse remodeling [21]. Thus, avoiding AVS disregards not only current recommendations [1], but also the overwhelming evidence of the superiority of AVS- over imaging-guided adrenalectomy in terms of both biochemical and of clinical outcome

[76,93].

Highlights	Class of Recommendation	Level of Evidence
• AVS is the key diagnostic step to identify patients to refer for unilateral laparoscopic adrenalectomy.	I	B
• AVS is recommended in all PA patients fulfilling certain requirements.	I	B
• AVS must be performed under well-standardized conditions, i.e. after correction of hypokalemia and switching the interfering medications.	II	B
• AVS can be performed by simultaneous or sequential cannulation, under basal or cosyntropin-stimulated conditions, following pre-defined protocols.	II	B
• The measurement of plasma cortisol, metanephrine or androstenedione concentration, must be used to establish success and calculate the lateralization index.	II	B

5.3. Alternative strategy for subtyping

A number of scores based on the clinical features of the patients, have been proposed to spare AVS in patients with a low prior probability of harboring a unilateral PA [94–96]. However, none have shown an accuracy high enough to justify their clinical use **(Class of Recommendation III, Level of Evidence C**). A more in-depth discussion of these strategies, including positron emission tomography with C^{11}methomidate, is available in the Supplemental Material.

6. Testing for familial forms of primary aldosteronism and detection of genetic mutations

In young patients diagnosed with PA, especially those with a family history of PA and/or stroke at young age, i.e. less than 40 years, familial forms of PA should be considered and confirmed, or excluded. Four familial forms of PA, named familial hyperaldosteronism type I to IV (FH–I to FH-IV) have been described thus far (Table 3). One additional germline mutation, has been identified with no family occurrence [12,96].

FH-I, also known as glucocorticoid-remediable aldosteronism, is an autosomal dominant disorder due to a hybrid chimeric gene deriving from a recombination between the CYP11B1 and CYP11B2 genes, which encodes an enzyme capable of synthesizing aldosterone under the control of ACTH [97]. In FH-1 the cells with the chimeric gene, which has ACTH-responsive elements regulating CYP11B2 transcription show a distribution throughout the adrenocortical zona fasciculata and are turned off by glucocorticoids. Diagnosis is made by long-PCR amplification of the hybrid gene [98].

FH-II is due to gain-of-function mutations in the CLCN2 gene coding for the chloride channel CIC-2 [99], which displays incomplete penetrance. Of note, mutations in this gene have been observed also in early-onset apparently sporadic cases of PA.

FH-III is caused by mutations in the KCNJ5 gene coding for the potassium channel Kir 3.4 [100]. Some cases display a very severe phenotype in infancy requiring bilateral adrenalectomy, but milder cases, which respond to medical therapy, have also been described [101].

FH-IV is determined by mutations in the CACNA1H gene encoding the calcium channel Cav 3.2 [102]. The disease phenotype displays incomplete penetrance in some kindreds; mutations in the same gene have been described in early-onset cases with PA.

A fifth form of PA, also known as PASNA (PA with Seizure and Neurologic Abnormalities) syndrome, because it features myoclonic seizures and severe neurological abnormalities besides PA, has been reported in two unrelated girls until now. It is due to due to germ-line to mutations in CACNA1D coding for the calcium channel CaV 1.3 [12]. Those suffering are unlikely to reproduce; therefore, its transmission is uncertain and its inclusion in FH provisional.

Other familial forms of PA will be discovered since there are families with PA, who showed none of the known mutations described above [103].

With the exception of FH-I, in all these genetic forms the mutated protein determines an alteration of the membrane potential, which leads to increased calcium entry and activation of a signaling cascade resulting in increased aldosterone production [104]. Diagnosis of these forms is made by sequencing of the candidate genes.

With exception of FH-I that responds to low-doses (0.5–1 mg) of dexamethasone, and of FH-III subtype A that requires bilateral adrenalectomy, all these forms are treated with MRAs, using blood pressure and plasma renin as proxy for up-titrating drugs.

Somatic mutations in KCNJ5, CACNA1D and in 3 other genes not involved in the pathogenesis of familial forms (ATP1A1, ATP2B3 and CTNNB1) have been associated with the pathogenesis of aldosterone-producing adenomas [101,104]. Somatic mutations in CACNA1D in small clusters of zona glomerulosa cells were suggested to play an important role in the autonomous aldosterone production in patients with BAH [105]. The routine search for somatic mutations in sporadic PA is currently confined to research, but might have a clinical impact in the future, since these mutations seem to be associated with a specific peripheral steroid profile. The latter might help the selection of patients for subtype invasive procedures such as AVS [106,107].

The discovery that in vitro macrolide antibiotics cell blunted aldosterone production in cells genetically engineered to harbor some KCNJ5 mutations [108], and in cells with the same mutations isolated *ex vivo* from APA, suggested the feasibility of a precision medicine approach to the medical treatment of PA [109], a hypothesis currently being tested in the MAPA Study [110].

Highlights	Class of Recommendation	Level of Evidence
• Five forms of PA due to germ-line mutations have been identified.	I	A
• Patients diagnosed with PA at a young age, with a family history of PA and/or early cerebro- and cardio-vascular events should be considered to have germ-line mutations.	I	B
• These patients should be tested for germ-line mutations.	I	B
• Genetic testing allows a specific and more effective treatment in FH-1.	I	B

7. Comorbidities

7.1. Obstructive sleep apnea

Studies with full overnight polysomnography to diagnose obstructive sleep apnea (OSA) reported a prevalence around 79% in PA patients, thus indicating that OSA is quite common in patients with PA [111,112]. In a recent cross-sectional study the prevalence of OSA in PA patients was 67% in both white and Chinese patients [113]. This can be because sodium and fluid retention in PA cause oedema of the upper airway soft tissues, thus worsening obstruction. Consistent with this view, treatment of PA with either MRAs or adrenalectomy lowered significantly both the apnea/hypopnea index (AHI) and the neck circumference in OSA patients [111].

Patients with OSA have also been reported to have a two-three fold higher risk of developing PA than patients without OSA [112]. Animal studies [114] suggested that this could occur because of hypoxia-induced increase of plasma endothelin-1, a known secretagogue of aldosterone [115].

Prospective studies of patients with resistant hypertension showed a 77% prevalence of OSA; moreover, 29% of them also had PA [116], thus

suggesting that both OSA and PA often coexist in these patients. As 24-h urinary sodium level was an independent predictor of severity of OSA in PA patients, aldosterone-driven salt and fluid retention might have a play in the development of OSA in resistant patients; moreover, dietary salt restriction could be a treatment strategy for reduction of OSA severity in such patients [117].

7.2. Atrial fibrillation

Arterial hypertension is a major risk factor for atrial fibrillation (AF) and between 50% and 90% of AF patients have hypertension [118–122]. Hyperaldosteronism is held to cause structural changes in the heart, i.e. inflammation, fibrosis, remodeling, hypertrophy, and functional and electrophysiologic alterations [123–125] that create the stage for AF.

PA patients were reported to have a highly significant 12-fold higher risk of AF than essential hypertensive patients [126]. In a recently completed prospective study that recruited consecutive hypertensive patients referred for evaluation of AF, 42% had PA [127], indicating that AF is a common clinical presentation of PA. Of note, surgically curable forms accounted for 48% of these cases.

Considering the excess of cardiovascular damage and events associated with AF and PA, and given that adrenalectomy, besides warranting cure or a marked improvement in the control of high BP in many PA patients, also lowered the risk of incident AF [128], and of recurrent AF in those who returned to sinus rhythm [21], we recommend that hypertensive patients with AF should be systematically screened for PA (see Table 3 of Supplemental Material) **(Class of Recommendation I, Level of Evidence B)**.

As regards prevention of AF with MRAs treatment, two meta-analyses showed a reduction of AF risk in MRAs-treated patients, as compared to untreated patients [129,130]. Moreover, eplerenone was shown to reduce the incidence of new onset AF in a randomized clinical trial in mild systolic heart failure patients, 64.5% of which had arterial hypertension [131].

In the longitudinal phase of the PAPY Study, adrenalectomy, but not medical treatment, lowered incident AF at long-term to the low rate seen in optimally treated essential hypertensive patients, thus confirming results of a smaller single-center long-term observational study [21,128]. Moreover, an observational large retrospective study showed that MRAs-based treatment lowered incident AF particularly when renin levels raised during treatment [132].

7.3. Cardiomyopathy

PA is associated with cardiovascular damage in excess of what expected on the basis of BP elevation. A high rate of left ventricular hypertrophy (LVH) in PA was independently reported in Japan [133] and Italy [134], and studies with densitometric analysis and MRI suggested the development of LV fibrosis [135,136].

The excess of plasma aldosterone correlated with LVH, and early diastolic dysfunction [137,138], left ventricular enlargement with evidence of subclinical systolic dysfunction [139], In a prospective study of patients who underwent left heart catheterization due to different cardiac diseases, those with AF and hypertensive cardiomyopathy showed an increased ARR [140]. The increase in LVH in PA patients was confirmed in a meta-analysis that compared patients with PA and essential hypertension [141]. According to a pilot study of APA patients this could occur because of a reversible form of hyperaldosteronism-induced cardiomyopathy, enhancing acquaporin-1 expression with ensuing cell water overloading altering ultrastructural integrity and causing impaired cardiomyocyte contraction and relaxation [142].

Regression of LVH was well documented after adrenalectomy [21,143]. It was also reported with medical treatment [144], but not in a larger study [21]. In surgically treated PA patients LVH regression involved an inward type of reverse remodeling [21]. Of interest, in two small-sized studies surgical treatment of PA has been associated with a decrease of myocardial fibrosis, as assessed by MRI or echocardiography [135,145].

From the practical standpoint, the finding of LVH and/or of a LV mass disproportionally high for the BP levels should prompt for the search of PA.

7.4. Renal and metabolic complications

PA implies an increased risk for renal disease [146,147], and metabolic disorders [148], via excessive activation of the mineralocorticoid receptors. The deleterious renal effects of PA first reported by Halimi and Mimran [149], have been confirmed in the PAPY study [150], which showed a higher estimated glomerular filtration rate (eGFR)-adjusted urinary albumin excretion (UAE) rate, as compared with primary hypertension, thus identifying patients at increased risk of progression to renal failure.

Although MRAs and surgical adrenalectomy are the recommended therapies for PA [1], whether they effectively reduce the risk for renal and metabolic diseases equally is not well understood. To date, available evidence is confined to short-term cohort studies, but there are no randomized clinical trials comparing unilateral adrenalectomy and MRAs. A retrospective cohort study reported that medically treated PA patients, who showed persistently suppressed renin, had a higher risk for incident cardio-metabolic outcomes (i.e. cardiovascular events, AF, diabetes, and death) compared to age-matched patients with essential hypertension [148]. Similarly, MRAs therapy for PA was found to be associated with a higher incidence of chronic kidney disease and a greater annual decline in eGFR, as compared to essential hypertensive patients [146]. Thus, current drug therapy for PA may fail to abolish the excess risk for these outcomes unless volume expansion is adequately corrected and high BP well controlled. At variance, no difference in risk for developing renal damage was found between surgically treated PA patients and essential hypertensive patients, suggesting that adrenalectomy may be superior to drug treatment in preventing chronic kidney disease in PA [146]. However a recent meta-analysis found no differences in cardiovascular events and renal function outcomes between PA patients treated with MRAs or adrenalectomy, but in the adrenalectomized patients there was a reduction in the number of antihypertensive agents needed to control BP [151]. A review of 46 studies that compared renal function parameters in PA and essential hypertensive patients showed a higher eGFR in the former than the latter patients [by 3.37 ml/min IQR (0.82–5.93)] and a more severe albuminuria [standard mean difference 0.55 (0.19–0.91)]. After treatment of PA a reduction in eGFR [−10.69 ml/min (−13.23; −8.16)] and albumin excretion, and an increase in serum creatinine were observed in both medically and surgically treated patients [147].

7.5. Bone metabolism

There is a bidirectional cross-talk [152] between the parathyroid and the adrenocortical zona glomerulosa that may increase cardiovascular damage and risk, and enhance bone alterations [153]. Experimental and clinical studies showed that hyperaldosteronism affects mineral homeostasis through a calciuretic effect causing hypocalcemia and resulting in secondary hyperparathyroidism leading to a reduction of bone mineral density (BMD), which can explain the increased risk of bone fractures in PA patients seen in a population-based study [154]. Patients with PA were recently reported to display more prevalent osteoporosis, lower BMD, lower trabecular bone quality and higher prevalence of vertebral fractures compared with patients with non-functioning adrenal adenoma [155,156]. In line with these data, patients with PA, especially those with APA, showed higher serum parathyroid hormone (PTH) levels than patients with essential hypertension, despite similar 25-OH vitamin D levels [157–159]; moreover, PTH levels fell with surgical or medical treatment

of PA [160–162].

Highlights	Class of Recommendation	Level of Evidence
• PA is often associated to OSA, cardiac remodeling, AF, renal, metabolic, and bone disease.	I	B
• Hypertensive patients with these comorbidities should be considered as potential cases of PA.	I	B
• Target treatment of PA can ameliorate the course of these conditions.	I	B

8. Treatment

Thus far, the treatment modalities for PA have been examined in more than 40 clinical observational studies [163–165], but no randomized clinical trials have compared the clinical outcomes of adrenalectomy and medical therapy in unilateral PA. Hard end-points, such as total and cardiovascular mortality [166,167], cardio- and cerebro-vascular events [144,166], arrhythmias, and AF incidence [128], were examined in some studies, but in most the primary outcome were cure or improvement of hypertension, and/or potassium normalization [168,169]. Some studies reported a better outcome and a decrease of the number and/or doses of antihypertensive drugs with adrenalectomy, as compared to medical therapy. Moreover, adrenalectomy was recently found to resolve resistant hypertension, sometimes leading to complete cure in the AVIS-2 Study [76]. Adrenalectomy was also reported to improve several indexes of quality of life [170].

On the whole, available evidences support the view that removal of the cause of aldosterone excess through adrenalectomy excision of the culprit adrenal gland should be the preferred option of treatment, while medical treatment is indicated in BAH or when identification of unilateral PA failed **(Class of Recommendation II, Level of Evidence B)**. Hence, for unilateral PA the standard of care in terms of safety and feasibility is AVS-guided unilateral *trans*-peritoneal or retro-peritoneal laparoscopic adrenalectomy, which warrants a complete biochemical success in more than 98% of cases and cure (in 40–50%) or partial clinical success in terms of lowering BP in another 40% [93,171–173]. Identified predictors of a good clinical response were age, sex, short duration of hypertension, and number of antihypertensive medications [174,175].

Laparoscopic surgery implies a short hospital stay and can be performed at a very low operative risk **(Class of Recommendation II, Level of Evidence B)**. Rarely it might be complicated by bleeding, thromboembolism, pneumothorax or hemothorax and may require transition to an open approach; the latter is preferred in the rare cases of aldosterone–producing carcinoma [176]. Of note, similar outcomes were reported in meta-analyses comparing *trans*-peritoneal and retro-peritoneal laparoscopic adrenalectomy [172,177–180].

Less invasive procedures and partial adrenalectomy, which is feasible also by robotic surgery, are emerging options to preserve remnant adrenal function and avoid adrenal insufficiency [181–183]. However, they should be guided by super-selective AVS, a sophisticated refinement of AVS that is currently performed in only few centers in Japan **(Class of Recommendation II, Level of Evidence C)** [184].

Interventional radiology adrenal gland ablation, a scar less procedure that is feasible under local anesthesia and controlled sedation [185], can play a role in the treatment of lesions not eligible for surgery due to patient's comorbidity or refusal of surgery [186,187]. Small retrospective non-randomized studies on percutaneous ablation techniques, including radiofrequency ablation, cryoablation, and chemical ablation with ethanol or acetic acid suggested similar operative morbidity and mortality rates as conventional laparoscopic adrenalectomy, with technical success rate ranging from 82 to 100% [188–190]. We recommend that the final decision for the best treatment must be taken by a multidisciplinary team involving clinicians (endocrinology/internal medicine), experienced surgeons, anesthesiologists, and interventional radiologists **(Class of Recommendation II, Level of Evidence B)**.

In preparation for surgery, arterial hypertension and hypokalemia must be corrected with use of MRAs and/or potassium supplementation. Correction of obesity is also advised in preparation for elective surgery [191], as in our experience need for post-operative stay in the intensive care unit and failure to remove the culprit adrenal completely, are more common in obese patients **(Class of Recommendation II, Level of Evidence C)**.

In few patients, transient postoperative hyperkalemia and increased serum creatinine may follow adrenalectomy [192,193], which implies the need for monitoring these parameters at follow-up [194].

Common reasons of failure to surgically cure PA are an inaccurate diagnosis, i.e. non AVS-guided adrenalectomy, and/or the concurrence of chronic kidney disease, and/or essential hypertension [195], which can involve up to 30% of the PA patients. A clinical prediction score has been developed [196]; young age, female sex, a short history of hypertension, a high number of antihypertensive medications requirement, and absence of vascular remodeling, and/or renal chronic kidney disease were found to be the strongest predictors of cure of hypertension [197].

MRAs, alone or in combination with other antihypertensive agents, are recommended in order to normalize BP and obtain normokalemia in PA patients with bilateral disease and in those with AVS-diagnosed unilateral PA who are not candidate for adrenalectomy **(Class of Recommendation II, Level of Evidence A)** [191].

Antihypertensive agents may be required to achieve BP control in both surgically and medically treated patients [191]. Spironolactone, canrenone, potassium canrenoate, and eplerenone (which is more selective, but weaker and shorter acting than the others) are the recommended medications. We recommend to up-titrate them to the highest tolerated daily dose (from 12.5 up to 100 mg, usually 25–50 mg), to accomplish BP control and normokalemia [198,199], as inadequate dosing may results in uncontrolled disease and excess cardiovascular risk **(Class of Recommendation II, Level of Evidence B)**. Plasma renin levels can be used as a guide to the appropriate dosing of MRAs in the patients who are not at BP and/or potassium target, as detection of low or undetectable renin levels is a straightforward indication that hyperaldosteronism was not controlled [132,148,200].

MRAs side effects, including gynecomastia and erectile dysfunction, are common, dose-dependent and often unbearable in men [201]. Eplerenone, which is more selective, is not yet approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of PA, but it is better tolerated because of less antiandrogen and progesterone-like effects.

Instructing the PA patients to diminish sodium intake is a fundamental step because it decreases the urinary potassium loss and may allow to use lower dose of the MRAs. Association of inhibitors of the epithelial sodium channel, as amiloride and triamterene, is also a valuable strategy to spare MRAs in the patients experiencing side effects. Newer non-steroidal MRAs with a better safety profile, such as apararenone, esaxerenone, and finerenone, are under investigation for the treatment of heart failure and chronic kidney disease and may be effective also in PA [202].

Aldosterone synthase inhibitors are also being tested: a pilot study with LCI699 showed a BP lowering effect in PA patients, but its low specificity for CYP11B2 (aldosterone synthase) relative to CYP11B1 (11betahydroxylase) has prevented its further clinical developments [203]. More selective CYP11B2 inhibitors, which might eventually provide an effective treatment for the multitude of PA with BAH are being

developed.

However, while adrenalectomy effectively lowered incident AF [128] and reversed damage to the target organs (such as the kidneys and heart), it remains to be conclusively proven in randomized clinical trials whether long-term medical treatment can be equally effective.

Highlights	Class of Recommendation	Level of Evidence
• AVS-guided laparoscopic adrenalectomy is the best treatment for unilateral PA.	II	B
• In preparation for surgery, arterial hypertension, hypokalemia, and obesity should be corrected.	II	C
• Transient postoperative hyperkalemia and increased serum creatinine may follow adrenalectomy in some patients.	II	B
• In bilateral PA patients and in those with AVS-diagnosed unilateral PA cannot be candidate for surgery or other operative interventions, MRAs, alone or in combination with other antihypertensive agents, are recommended in order to normalize BP and obtain normokalemia.	II	A
• Medical treatment should be based on MRAs including spironolactone, canrenone, potassium canrenoate, and eplerenone.	II	B

9. Follow-up

In patients who underwent adrenalectomy for unilateral PA starting, we advise to withdraw or reduce antihypertensive therapy affecting plasma aldosterone and renin levels, and to stop potassium supplementation if possible, on post-operative day 1 [204]. Potassium should be measured shortly after surgery [205], and aldosterone and renin should be measured at least at one month and 6 months after surgery to confirm biochemical cure **(Class of Recommendation II, Level of Evidence B**), a simplification over what recently suggested [93], because by these times biochemical and clinical cure, if accomplished, are usually evident.

In patients who underwent AVS-guided adrenalectomy, biochemical success defined as correction of hypokalemia and hyperaldosteronism approaches 100% [21,77]. The BP outcome was differently stratified in different studies; for example as *cure, marked improvement, mild improvement or no improvement* in the AVIS-2 Study or as *complete, partial, and absent success*, in the PASO Study [77]. However, as BP is a highly complex phenotype and since high BP values can persist because of superimposed essential hypertension in spite of biochemical cure, or can fall independent of it, for example because of incident LV dysfunction or due to lifestyle changes, we favor biochemical over BP measurement to assess outcome. Moreover, when judging the clinical outcome, one should also consider the hypertension-mediated organ damage (HMOD) regression/progression and cerebro- and cardiovascular complications.

Short- and long-term periodical biochemical retesting is, therefore, necessary at least in the first six months, because confirmation of the diagnosis of APA requires demonstration of biochemical cure of PA after surgery. Persistence of PA indicates either a bilateral disease or, more commonly removal of the non-culprit adrenal, which occurs more commonly when surgery was not AVS-guided or, much more rarely, recurrence of and aldosterone-producing carcinoma [206].

In those patients with BAH allocated to life-long medical treatment biochemical retesting is also advised as the persistence of low plasma renin can be a proxy of insufficient MRAs dosing as discussed above.

In summary, we recommend biochemical follow-up data to prove the cure or failure of surgery, and a comprehensive clinical assessment based on HMOD (Table 4) **(Class of Recommendation II, Level of Evidence B**).

Table 3
Clinical and molecular classification of primary aldosteronism due to germ-line mutations [10].

Type	Prevalence %	Cytogenetic Location	Gene Mutation	Transmission	CT Findings	Treatment	Drug-Resistant Hypertension	Clinical Features
FH-I	0.5–1	8q24	CYP11B2/CYP11B1, Chimeric	Autosomal dominant	BAH or APA	Low-dose dexamethasone	Possible (with drugs other than dexamethasone)	Early-onset PA, hybrid steroids, cerebrovascular events
FH-II	<1	3q27	CLCN2 (R172Q, M22K, G24D, S865R, Y26 N)	Autosomal dominant	BAH or APA or no adrenal, abnormalities	MRAs	No	Early-onset PA
FH-III	<0.5	11q23	KCNJ5 (T158A, I157S, E145Q, G151E, Y152C)	Autosomal dominant	BAH or no adrenal abnormalities	Bilateral, Adrenalectomy or MRAs	Yes	From mild PA form to severe early-onset PA
FH-IV	n.a.	16p13	CACNA1H (M1549V, S196L, P2083L, V1951E)	Autosomal dominant	Little or no adrenal, abnormalities	MRAs	No	Early-onset PA, mental retardation, social and development disorders
PASNA syndrome	n.a.	3p14.3	CACNA1D (I770 M, G403D)	Unknown	No adrenal abnormalities	Calcium channel, Blockers and MRAs	No	Early-onset PA, seizures, neurological abnormalities. No family occurrence reported thus far

FH, familial hyperaldosteronsim; PASNA, PA with Seizure and Neurologic Abnormalities; CT, computed tomography; BAH, bilateral adrenal hyperplasia; APA, aldosterone producing adenoma; MRAs, mineralocorticoid receport antagonists; PA, primary aldosteronism; n.a., not available.

Table 4
Assessment of hypertension-mediated organ damage in PA patients.

Comorbidity	Basic clinical screening	Instrumental and biochemical evaluation
Obstructive sleep apnea	History of snoring, excessive daytime sleepines, nocturnal cough, headach, etc.	Validated questionnaires (i.e. STOP-Bang and NoSAS); home sleep apnea testing (HSAT); attended full overnight polysomnography (PSG)
Atrial fibrillation	History of palpitations, arrhythmias, dyspnea.	12-lead ECG, Holter monitoring, Echocardiography
Cardiac remodeling, left ventricular hypertrophy	Hystory of chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, syncope, heart failure.	12-lead ECG, Echocardiography
Metabolic disease	Hystory of non type 1 diabetes, insuline-resistance	Fasting blood glucose and glycated HbA1c
Renal function and chronic kidney disease	History of polyuria, nocturia, haematuria, urinary tract infections.	Urinary albumin excretion (UAE), estimated glomerular filtration rate (eGFR)

Highlights	Class of Recommendation	Level of Evidence
• A strict clinical and biochemical follow-up is mandatory in the first 6 months in all PA patients after surgical or medical treatment.	**II**	**B**
• The complete cure of hypertension after adrenalectomy is more frequent in young women and in patients with short history of disease.	**II**	**B**
• The persistent or recurrent hypertension after proper treatment is more common in older PA patients, in those with longer history of hypertension, or in not AVS-guided diagnosis of unilateral PA.	**II**	**B**

10. Conclusions

As a potential curable cause of hypertension PA should always be suspected in hypertensive patients and identified in a cost-effective manner by all physicians dealing with such patients. Screening for PA is particularly beneficial when hypertension is severe and/or resistant to treatment, because target treatment and/or surgery allows to bring BP under control, to withdraw or markedly reduce the number and dosage of antihypertensive medications, and to prevent or regress organ damage and associated comorbidities.

Subtyping should be performed at third level referral centers that are proficient in performing and interpreting AVS. Adrenalectomy usually cure hyperaldosteronism and hypokalemia when a unilateral cause of PA is discovered. BP can also be normalized or considerably reduced in a substantial proportion of patients. Even when subtyping is unfeasible or failed, identification of BAH allows undertaking a target treatment, which will provide better control of high BP.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2020.100029.

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