Endocrine
https://doi.org/10.1007/s12020-024-03773-9

REVIEW

Practical consensus for the treatment and follow-up of primary aldosteronism: a multidisciplinary consensus document

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Received: 6 February 2024 / Accepted: 7 March 2024
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Abstract

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension and is associated with a higher cardiometabolic risk than essential hypertension. The aim of this consensus is to provide practical clinical recommendations for its surgical and medical treatment, pathology study and biochemical and clinical follow-up, as well as for the approach in special situations like advanced age, pregnancy and chronic kidney disease, from a multidisciplinary perspective, in a nominal group consensus approach of experts from the Spanish Society of Endocrinology and Nutrition (SEEN), Spanish Society of Cardiology (SEC), Spanish Society of Nephrology (SEN), Spanish Society of Internal Medicine (SEMI), Spanish Radiology Society (SERAM), Spanish Society of Vascular and Interventional Radiology (SERVEI), Spanish Society of Laboratory Medicine (SEQC(ML)), Spanish Society of Anatomic-Pathology and Spanish Association of Surgeons (AEC).

Keywords Primary aldosteronism · Adrenalectomy · Biochemical cure · Hypertension · Spironolactone · Eplenerone

In representation of the following medical Spanish societies: Spanish Society of Endocrinology and Nutrition (SEEN), Spanish Society of Cardiology (SEC), Spanish Society of Nephrology (SEN), Spanish Society of Internal Medicine (SEMI), Spanish Radiology Society (SERAM), Spanish Society of Vascular and Interventional Radiology (SERVEI), Spanish Society of Laboratory Medicine (SEQC(ML), Spanish Society of Anatomic-Pathology (SEAP), Spanish Association of Surgeons (AEC).

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Published online: 20 March 2024

Keypoints

- The treatment of choice for PA is medical therapy with mineralocorticoid receptor blockade for bilateral cases and unilateral adrenalectomy for unilateral PA.
- The goals of PA treatment are to normalize blood pressure (BP) and excessive aldosterone production, with the final aim of improving associated comorbidities and reducing mortality.
- Spironolactone is usually the mineralocorticoid receptor antagonist (MRA) of choice for medical treatment of PA. However, eplerenone has a similar efficacy to that of spironolactone when used in doses 2–3 times higher than the latter and administered 2–3 times a day.
- Eplerenone has the advantage of not inducing the anti-androgenic side effects commonly seen with spironolactone.
- Adrenalectomy is the gold standard procedure used to remove the aldosterone-hypersecreting adrenal tissue.
- The Primary Aldosteronism Outcome (PASO) group criteria are recommended for defining the control objectives of biochemical and clinical response to treatment.

Introduction

Primary aldosteronism (PA) is considered the main cause of secondary hypertension (HT) [1]. PA prevalence has been underestimated due to its high clinical similitude with primary HT, save in the cases in which the presence of hypokalemia leads to screening for PA [1]. Patients with PA have a higher rate of cardiovascular morbidity and mortality than patients of the same age and sex with primary HT and the same degree of blood pressure (BP) elevation [2]. A recent meta-analysis [2] of 31 studies, including 3838 patients with PA and 9284 patients with essential HT, described an increased risk of stroke (odds ratio [OR] 2.58), coronary artery disease (OR 1.77), atrial fibrillation (OR 3.52) and heart failure (OR 2.05) in PA patients compared to essential hypertensive patients. In addition, the diagnosis of PA increased the risk of diabetes (OR 1.33), metabolic syndrome (OR 1.53), and left ventricular hypertrophy (OR 2.29) [2].

Targeted drug treatments are available for PA and are effective in controlling BP and reducing associated cardiovascular risk. Spironolactone, a potent mineralocorticoid receptor antagonist (MRA), is normally the first line of medical treatment for PA [1, 3]. In case of intolerance to spironolactone, eplerenone is usually used as a second-line therapy. In addition, a significant percentage of PA cases –when unilateral– can potentially be cured with surgical treatment. Unilateral adrenalectomy is the main procedure used to remove the aldosterone hypersecreting adrenal tissue, leading to a reduction in the cardiometabolic risk associated to aldosterone hypersecretion [4]. Surgical options include open strategy or minimally invasive surgery (laparoscopic or robotic techniques) [1, 5, 6]. Recent advances in immunohistochemistry diagnosis of adrenal tumors following the development of CY11B antibodies has dramatically changed the view of the adrenal fasciculate and glomerular cortex [7, 8]. PA follow-up is also an important point in patients with PA, however, there is little consensus on how it should be done, being a subject that is hardly mentioned in the different clinical guidelines [1, 5, 6]. The objectives of control with medical and surgical treatment are generally based on the recently published by the Primary Aldosteronism Outcome (PASO) Group [9], where they established clinical and biochemical criteria. Still, their relevance as regards hard cardiovascular endpoints has yet to be validated.

For the optimal management of PA, a multidisciplinary team of different surgical and medical specialties that work together from their respective roles for the treatment and follow-up of PA is essential. Herein we provide a practical guideline elaborated following the Agree II Guideline [10] in a nominal group process from the perspective of experts from the national societies of the different disciplines involved, respectively the Spanish Society of Endocrinology and Nutrition (SEEN), Spanish Society of Cardiology (SEC), Spanish Society of Nephrology (SEN), Spanish Society of Internal Medicine (SEMI), Spanish Radiology Society (SERAM), Spanish Society of Vascular and Interventional Radiology (SERVEI), Spanish Society of Laboratory Medicine (SEQCML), Spanish Society of Anatomic-Pathology (SEAP) and Spanish Association of Surgeons (AEC) with the aim of creating a series of recommendations that facilitate the treatment, pathology examination and follow-up of patients with PA. Evidence has been searched for in international guidelines, consensus statements, systematic reviews, and primary studies to formulate our recommendations and include the recommendations with strong evidence in this practical guideline.

Due to the extension of the consensus, the epidemiology, clinical and biochemical diagnosis, and subtype classification of PA have been addressed in another article (first part of the consensus) [11].

Treatment

Patients with bilateral PA should be medically treated with mineralocorticoid receptor blockade, whereas for unilateral PA, the treatment of choice is unilateral adrenalectomy (Fig. 1).

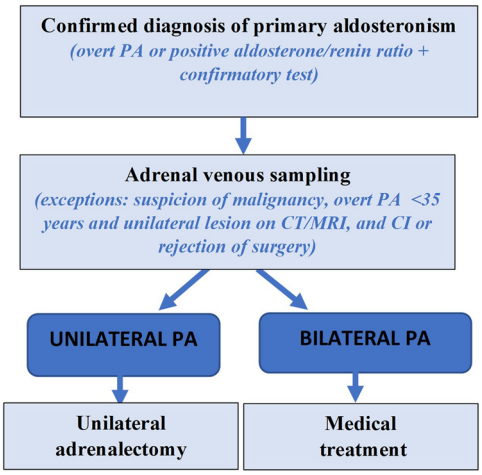

Fig. 1 Proposed Flow diagram for the treatment of primary aldosteronism. CI contraindications, CT computer tomography, MRI magnetic resonance, PA primary aldosteronism

The goals of the PA treatment are to normalize BP and to mitigate the deleterious effect of the excessive aldosterone production, with the final aim of improving the associated comorbidities and quality of life and reducing mortality.

Medical treatment

The pharmacological management of PA has as its main objectives the control of organ damage (mainly at the cardiovascular and renal levels) and the morbidity and mortality derived from aldosterone excess and HT, as well as the correction of hypokalemia. The main drugs used for this purpose are MRA, which have been shown to be effective for BP control and correction of the effect of the aldosterone excess [12]. It seems that in more than 60% of PA cases, medical treatment is chosen over surgical treatment, mainly due to the technical and interpretation difficulties of adrenal venous sampling (AVS) for surgical planning and due to the high prevalence of advanced age at diagnosis (around 5–10% of cases) [13]. In this regard, the AVSTAT study, a retrospective, multinational, multicenter questionnaire-based survey of management of PA patients from 16 centers, described a rate of AVS implementation of 66.3%, with a successful AVS rate of 89.3% and of unilateral disease of 36.9%, in a cohort of 4818 patients with PA [14]. Thus, despite the high rate of successful AVS in this study, approximately 30% of the cases did not undergo AVS and of the cases with a successful AVS study, only 37% were unilateral PA cases.

Indications

Bilateral adrenal hyperplasia is known to account for half of the PA cases. The difficulties involved in performing a bilateral adrenalectomy, as well as the need for lifelong gluco- and mineralocorticoid replacement therapy, make medical treatment the first choice. Unilateral adrenalectomy can be considered in severe scenarios or in the case of marked adrenal asymmetry in imaging studies [15, 16]. Medical treatment should be considered in those clinical scenarios in which bilateral disease has been determined or if surgery and, therefore, AVS has been discarded due to other clinical conditions. The point regarding the need for AVS before surgery might be a limitation for the indication of surgery since it is a procedure that requires an adequate preparation of the patient, which is not simple on many occasions and is difficult to interpret by non-experts [17, 18]. In addition, the technique is complex and subject to complications [17, 18]. Regarding advanced age, although surgical treatment can be considered, the higher rate of comorbidities in this population and the possibility of lower efficacy in terms of long-term control of HT must be considered. Medical treatment with MRA is the overall indication for genetic forms of PA. A particular case is that of glucocorticoid-remediable hyperaldosteronism or familial hyperaldosteronism type 1, in which treatment must consist in the administration of dexamethasone or prednisone, preferably at night, to partially suppress ACTH secretion by the pituitary gland. In these instances, the lowest effective dose of glucocorticoid should be used to control BP and plasma potassium level. The addition of an MRA should be considered if treatment goals are not achieved [12] (Table 1).

Table 1 Indications of medical treatment in primary aldosteronism

Indications of medical treatment in PA
Bilateral Adrenal Hyperplasia
Hereditary Disorders
Unilateral Adrenal Adenoma with high surgical risk
Contraindication for surgery
Patient rejection
Non-conclusive AVS
Advanced age (>65/70 years) *
Pregnancy**
Inability to perform AVS

*In patients with good quality of life, surgical treatment should be considered when unilateral PA has been confirmed

**In pregnant patients with severe PA manifestations in the second trimester, the performance of a unilateral laparoscopic adrenalectomy could be considered

AVS adrenal venous sampling

Available treatments

As previously stated, the main drugs used in PA are MRAs, with spironolactone normally the initial drug. Eplerenone, not yet approved worldwide, has been shown to be similar

Table 2 Medical treatment of primary aldosteronism [24]

Drug	Mechanism of action	Starting dose and maximum doses	Secondary side effects
Spironolactone	Nonselective and competitive MRA	25–50 mg/24 h Maximum: 400 mg/24 h	Hyperkalaemia; Gynecomastia and impotency in males; menstrual irregularities in women. Gastrointestinal side effects
Eplerenone	Selective and competitive MRA	50 mg/12 h Maximum: 200–300 mg/24 h	Hyperkalaemia
Amiloride	Epithelial sodium channel blocker	2.5–10 mg/12 h Maximum 10 mg/12 h	Hyperkalaemia; Gastrointestinal side effects
Triamterene	Epithelial sodium channel blocker	100 mg/12 h Maximum 150 mg/12 h	Gastrointestinal side effects

MRA mineralocorticoid receptor antagonist

in efficacy to that of spironolactone when used in doses 2–3 times higher than the latter when administered 2–3 times a day. Eplerenone lacks the anti-androgenic side effects of spironolactone, and could therefore, when available, be the drug of choice in men, given their high rate of non-compliance with spironolactone therapy.

Moreover, new drugs that inhibit aldosterone synthesis and could be viable alternatives to MRAs in the near future are being developed.

As in all patients with HT, avoiding the consumption of alcoholic beverages and performing aerobic physical exercise on a regular basis reduces the risk of therapeutic failure [19]. Below, we indicate the main drugs used and their characteristics (Table 2):

- *Spironolactone:* Is considered the drug of choice in PA. However, given the high rate of antiandrogenic side effects seen with spironolactone use, eplerenone might be preferable, particularly in men. In this regard, spironolactone related gynecomastia was in 61 (10%) of 603 of males at a dose of 25 mg/day spironolactone in the RALES study [20] and in up to 52% at doses of 150 mg/day and higher in other series [21]. Other secondary side effects include gastrointestinal symptoms, muscle cramps, and a decreased libido (more common in men). Its efficacy in BP control has been demonstrated, mainly reducing systolic BP (around 40–60 mmHg) and being effective in monotherapy to maintain BP < 140/90 mmHg in 50% of patients [22]. An initial dose of 25–50 mg/day can be used and up-titrated to a maximum of 400 mg/day [23]. It has a prolonged pharmacological action, which allows its administration in a single daily dose. In elderly patients and in those with reduced kidney function, a starting dose of 12.5 mg/day is recommended.
- *Eplerenone*: Eplerenone, not yet approved worldwide, has been shown to be similar in efficacy to that of spironolactone when used in doses 2–3 times higher than the latter when administered 2–3 times a day without the anti-androgenic side effects. The initial dose can be between 50–100 mg twice a day [1] and the maximum established dose is 200–300 mg/24 h in divided doses [24]. It is metabolized in the liver by CYP3A4, a member of cytochrome P450, so possible pharmacological interference should be considered.

In patients with stage 3 chronic kidney disease (CKD), MRA should be used with caution, due to the risk of hyperkalemia, and must be avoided when the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m².

- *Amiloride and triamterene* are both distal tubule sodium channel antagonists, where aldosterone performs some of its actions; both function as potassium-sparing diuretics and therefore exert beneficial effects on HT and hypokalemia. Amiloride has been the most studied in PA, with a smaller confirmed potency than MRAs on BP [22]. Both amiloride and triamterene are generally used for MRA-related adverse effects.
- *Others:* both angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor antagonists (AIIRAs), and calcium antagonists have beneficial effects on BP and can be used as complementary treatments to those previously mentioned. They can play an important role in reducing the dose of spironolactone and, as a result, in its possible side effects [1].
- During pregnancy, alpha-methyl-dopa is the drug of choice, due to the risk of fetal feminization with spironolactone and due to the lack of studies with eplerenone.

Surgical treatment

Once the diagnosis of PA has been established, it is essential to distinguish between unilateral and bilateral disease since the former can be cured by surgical removal of the affected adrenal gland, which is why unilateral PA is the

primary surgical indication. In contrast, patients with bilateral disease are mainly treated medically with MRA, as bilateral adrenalectomy is associated with high morbidity and low cure rates, making this indication extremely rare. Therefore, the success of the treatment lies, first of all, in establishing a proper diagnosis of lateralization [1, 25].

The procedure's objective is to remove the hypersecretory aldosterone tissue from the adrenal gland. However, prior to surgery, proper preoperative management is essential to control both HT and hypokalemia. Four to six weeks of treatment prior to surgery with MRA and potassium supplements to achieve BP levels <140/90 mmHg and normokalaemia may be advisable, particularly if spironolactone has been used.

Total adrenalectomy is the gold standard procedure used to remove the hypersecretory aldosterone tissue. Surgical options include open or minimally invasive surgery (laparoscopic or robotic techniques) using an anterior, lateral, or posterior approach. Minimally invasive surgery is preferred over an open strategy and is also the most extended approach worldwide. Among them, laparoscopic adrenalectomy via posterior or lateral transabdominal approach is the most frequently used. Technical details of both procedures do not differ from other adrenalectomies, and both are conducted under general anesthesia [26]. Laparoscopic lateral transabdominal adrenalectomy is performed with the patient in lateral decubitus position and flexing the operating table at the waist to open the space between the lower rib and the iliac crest. Three or four ports are used, and a great operating field is obtained. Some degree of liver, spleen, or pancreas tail mobilization are required to reach the retroperitoneum, which has been described as its main disadvantage [26, 27]. Retroperitoneal access is performed in a modified prone position. The operating table is flexed to accentuate the space between the costal margin and the iliac crest, and three ports are used. Its main advantages are that it provides a direct approach to the adrenal gland avoiding visceral mobilization and intraperitoneal adhesions. However, it is technically demanding due to the unusual anatomical view and narrow working space [26, 27]. Although both approaches have proven to be effective in terms of adequate resection and minimal morbidity, some studies have shown a slight superiority in the retroperitoneal approach in terms of shorter surgery extent, lower blood loss and postoperative pain, faster recovery, and the elimination of the risk of surgical access site herniation whereas conversely, a high level of expertise in adrenal surgery is required [28–30].

BP levels improve in the first 6 months after the treatment, and surgical series report good results if the adequate indication has been performed: 94% biochemical remission and 41% partial clinical resolution (hypokalemia and HT), while only 42% achieve total resolution (i.e, cure of hypertension) [9, 31]. Both left ventricle and intima carotid artery thickness improve considerably after surgery. Worse outcomes are observed in long-standing PA, indicating the importance of early diagnosis and treatment [32]. Regarding recurrence, to date, only a few reports have described PA recurrence after unilateral adrenalectomy with complete clinical and biochemical success [33–35]. In this sense, Citton et al. reported that 3.7% of patients with biochemically cured PA experienced recurrence after a mean follow-up of 64 months [34]. A more recent study found that up to 23% of PA cases classified as biochemically cured at short-term follow, experienced biochemical recurrence after a median of 89 months of follow-up. The risk of recurrence was significantly higher in patients with nonclassical PA histopathology (60% of nonclassical histopathology versus 14% with classical histopathology; $P = 0.005$) [35].

Although the most extended technique is unilateral total adrenalectomy, subtotal adrenalectomy could be used in highly selected cases with proper indications and when technically feasible. This last approach could be associated with high failure rates, specifically in non-localized unilateral PA different from typical aldosterone producing adenomas (APAs), mainly unilateral adrenal hyperplasia (with an incidence around 10–36% of PA) and multiple unilateral APAs (with an incidence around 5–10.2% of PA). Thus, although a recent metanalysis reports a recurrence rate with partial adrenalectomy of only 2% when applied properly, this indication should be regarded cautiously [36]. In this regard, in general adrenal-sparing nodulectomy should be avoided since it is associated with recurrence, unless super-selective AVS is performed. Nonetheless, super-selective AVS requires more expertise and time, and it has been considered of special benefit in patients with bilateral or recurrent APA with the aim of proposing partial adrenalectomy allowing the preservation of non-tumorous glandular tissue [37].

In the last decade, other percutaneous treatment modalities have emerged, such as microwaves or radiofrequency ablation (RFA). RFA is the most widespread, and several retrospective series have shown that this is a safe procedure in expert hands. But when comparing the results of RFA to minimally invasive surgery, although RFA was less invasive, HT cure and BP control were better achieved in the surgery group. Moreover, patients in this group require fewer antihypertensive drugs than patients who had undergone RFA. Therefore, RFA should be reserved for patients who are unable to undergo surgery (advanced age and/or high surgical risk) or who refuse surgery [38, 39].

Pathology study

Removal of the entire adrenal gland, including nodular lesions and apparently normal parenchyma, is recommended

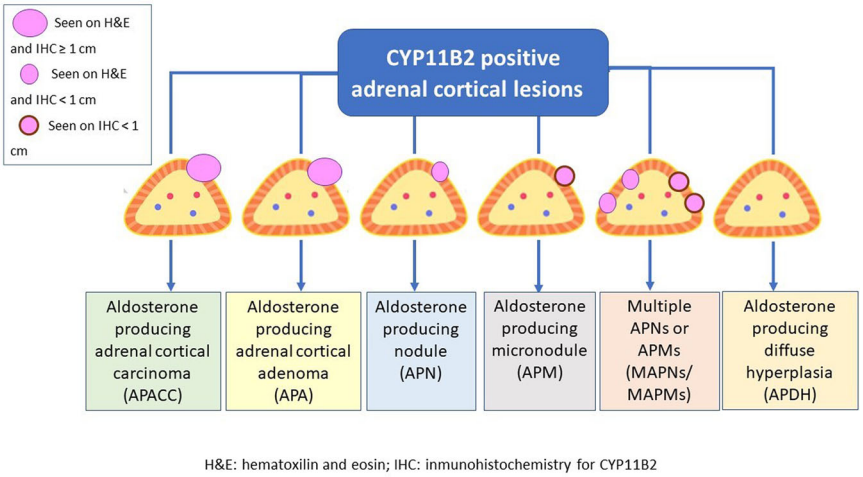

Fig. 2 Classification of PA associated adrenal lesions by the International Histopathology Consensus for Unilateral Primary Aldosteronism (HISTALDO) [42]. H&E haematoxylin-eosin stain, IHC immunohistochemistry for CYP11B2

for an adequate morphological evaluation, although laparoscopic methods may lead to fragmented specimens [40]. Macroscopic description, fixation and processing procedures are available in many standardized protocols for adrenal cortical lesions [8, 41]. APAs, especially those harboring KCNJ5 mutations, typically have a canary (golden) yellow appearance [40]. Submitting the whole specimen for histopathological examination after sectioning the longer axis perpendicularly is mandatory. Nodules must be sectioned and measured at their largest diameter for a proper classification [7]. Histopathological alterations found in patients with PA can affect adrenal glands as a unilateral or bilateral disease [7]. Adrenal cortical carcinoma (ACC) is an extremely rare cause of PA [40], so the vast majority of alterations will correspond to benign diseases.

Aldosterone is produced by aldosterone synthase (CYP11B2), physiologically located in the zona glomerulosa. The recent development of monoclonal antibodies against this enzyme has allowed the immunolocalization of aldosterone-producing cells [42], transforming the perspective of the adrenal pathology examination. Its application has led to the proposal of a new classification scheme by the International Histopathology Consensus for Unilateral Primary Aldosteronism (HISTALDO) [7] (Fig. 2), combining morphology and immunostaining methods. This new classification scheme, endorsed in the new WHO classification of tumors of the Endocrine Organs [42], can predict the risk of recurrence after unilateral resection [7]. This classification includes six diagnostic categories: aldosterone-producing cortical carcinoma, aldosterone-producing cortical adenoma, aldosterone-producing nodule, aldosterone-producing micronodule (previously known as cell clusters), multifocal aldosterone-producing nodules and/or micronodules, and aldosterone-producing diffuse hyperplasia, all of them CYP11B2-positive to immunostaining (Fig. 2). Adenomas, respectively APAs, are considered benign neoplasms measuring ≥1 cm, while nodules are lesions under 1 cm that can be distinguished with a hematoxylin-eosin stain. Micronodules correspond to lesions under 1 cm that are only identifiable by immunohistochemistry. Aldosterone-producing diffuse hyperplasia is applied when more than 50% of the zona glomerulosa layer shows continuous CYP11B2-positive hyperplasia [7, 43].

Solitary APAs and nodules are considered as classical histology findings, whereas multifocal nodules/micronodules and diffuse hyperplasia are considered as non-classical histology features. This distinction is relevant, as biochemical recurrence is observed in 42% of patients with non-classical histology, while it occurs in less than 5% in cases with classic histology [7].

Some cytomorphological features can be correlated to some genotypes related to the origin of the disease: clear cell predominant morphology is observed in KCNJ5-mutant adenomas and nodules, with mutations in this ion channel being the most frequently identified. On the contrary, KCNJ5 wild type lesions show a predominant compact cell morphology [42, 43].

In cases treated with spironolactone, eosinophilic concentrically laminated electron dense inclusions can be observed, known as spironolactone bodies. They can be identified in adenomas as well as in the zona glomerulosa of the adjacent adrenal cortex [40].

Follow-up

Regular follow-up is mandatory in both surgery and medically treated PA forms (Fig. 3A, B).

Objectives

For surgical treated PA, we subscribe to the control criteria of biochemical and clinical response to treatment as reported by the Primary Aldosteronism Outcome (PASO) group [9] (Table 3).

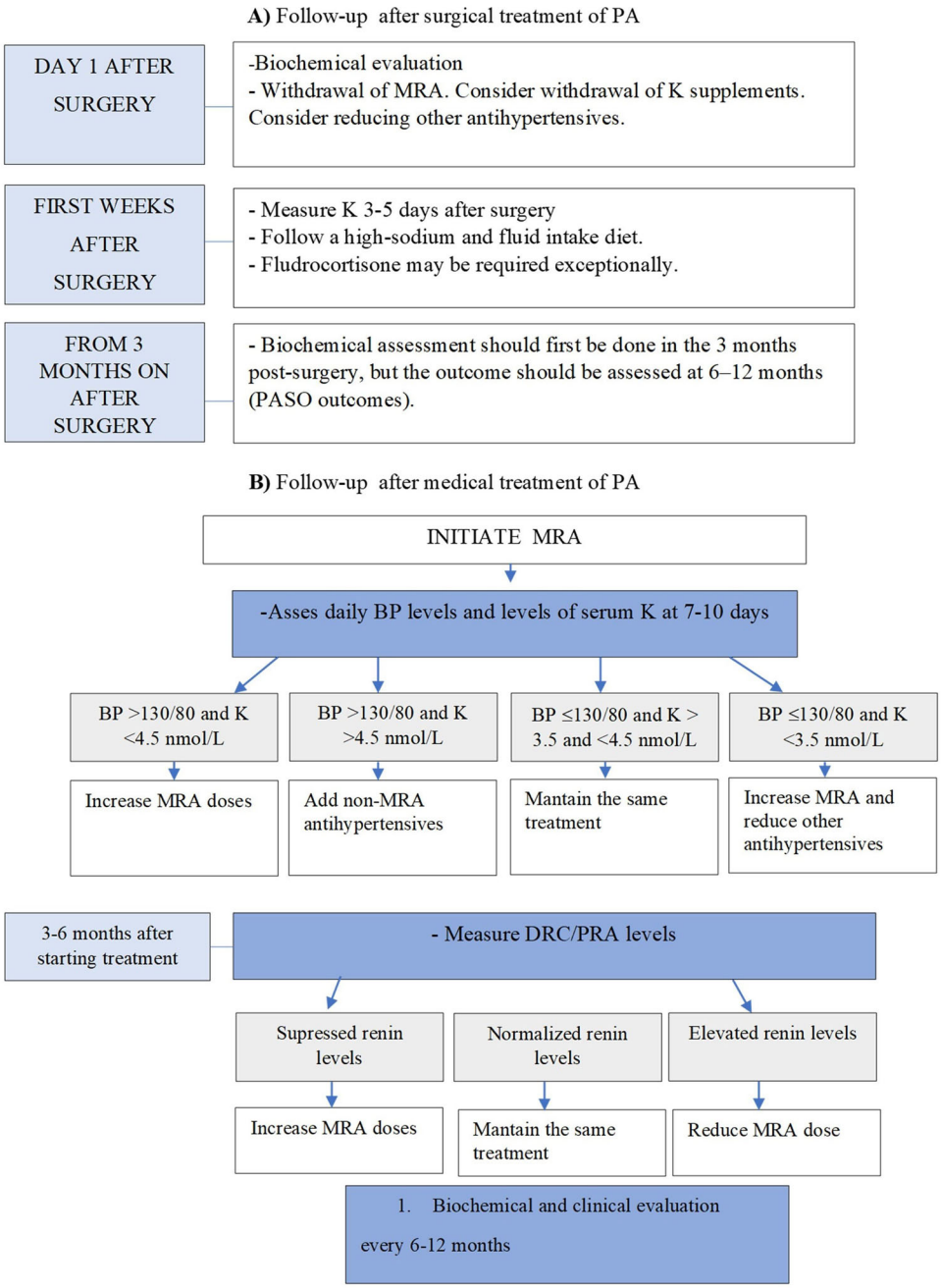

Fig. 3 Recommendations for follow-up of patients with primary aldosteronism (PA): (**A**) Follow-up after surgical treatment of PA; (**B**) follow-up after medical treatment of PA [19]. *if side effects, change spironolactone with eplerenone. MRA mineral receptor antagonists, BP blood pressure, PRC/PRA plasma renin concentration/plasma renin activity

Specific considerations for the post-surgical follow-up

In most cases, surgery corrects hypokalemia, improves HT control, and reduces the burden of drug therapy, and in about 40% of cases, adrenalectomy resolves HT [44].

- ***Short-term follow-up*** [45]

  - Shortly after surgery plasma aldosterone concentration (PAC) and plasma renin activity (PRA) or direct plasma renin concentration (DRC) should be measured to assess biochemical response. However, sometimes renin levels are slow to change. As when performing the screening ARR of diagnostic tests, at least 4 weeks should pass before measurement of aldosterone and renin levels, to allow the effect of prior MRA to pass.

  -On postoperative day 1:

  - MRA should be discontinued, and potassium supplementation can be withdrawn as a function of kalemia (the genomic action of aldosterone can persist for up to 3 days).

  - The risk of severe hypokalemia induced by isotonic saline in hyperaldosteronism patients may persist approximately until day 2–3 after surgery. During this time, iv isotonic saline should be avoided or minimized

Table 3 Definition of surgical outcomes in primary aldosteronism

Clinical biochemical		
Complete Success (Remission)	Normal BP without antihypertensive medication	1. HypoK correction (if present before operation) and 2. Normalization of ARR or 3. Aldosterone suppressed during confirmatory testing if ARR increased postoperatively
Partial Success (Improvement)	Stable BP with less antihypertensive medication or lower BP with an equal or less number of antihypertensive drugs	1. Correction of hipoK (if present before surgery) and increased postoperative ARR and 2. Decreased ≥50% in basal aldosterone levels or 3. Abnormal but improved postoperative aldosterone during confirmatory testing
Absence of Success (Persistence)	Unchanged or higher BP with equal or greater n° of antihypertensive drugs	1. Persistent hypoK (if present before operation) or 2. Persistent increase in ARR after surgery and 3. Failure to suppress aldosterone secretion during confirmatory testing

BP blood pressure, *hipoK* hypokalemia Confirmatory tests refer to saline infusion test, oral sodium loading test, fludrocortisone suppression test, or captopril test, *ARR* aldosterone-renin -ratio

Clinical and biochemical cure is, moreover, a demonstration of the unilateral nature of PA, and, respectively, of PA

the first 2 days after surgery.

-During the first weeks after surgery:

- A high sodium and fluid intake should be recommended to avoid hyperkalemia due to rebound hypoaldosteronism from the chronic suppression of the contralateral adrenal gland [46].

- Serum potassium should be measured following surgery and 3 to 5 days after surgery. Severe hyperkalemia after adrenal surgery is more frequent in prolonged contralateral hypoaldosteronism, occurring in 5% of PA cases. Persistent aldosterone insufficiency requires long-term fludrocortisone treatment. In case of severe hyperkalemia, emergency in-patient treatment is needed, including increased fluid and salt intake, isotonic saline administration, forced diuresis, and, if necessary, standard hyperkalemia emergency care algorithms.

- Temporary treatment with fludrocortisone may be considered, if necessary, as mentioned above.

BP usually normalizes or shows maximum improvement 1 to 6 months after unilateral adrenalectomy for unilateral APA but may continue to decline for up to 1 year in some patients.

-From 3 months on after surgery: Outcome assessment should be done initially 3 months after surgery, but the outcome should be assessed at 6–12 months.

Other considerations: Almost one quarter of the patients with PA co-secreting cortisol can develop adrenal insufficiency. In this situation we recommend starting glucocorticoid replacement therapy during or after adrenalectomy and optimization of the dose and duration of the replacement depending on the severity of autonomous cortisol co-secretion [46].

- ***Long-term follow-up***

Clinical and biochemical outcomes should be reassessed annually [7]. Younger patients (especially women) are more likely to have complete biochemical and clinical or partial clinical cures after surgery, probably due to the shorter duration of HT and the known vasoprotective role of estrogens in premenopausal women [47].

Patients with an elevated body mass index have a lower chance of being cured of PA at a clinical or biochemical level. This is probably due to their higher PAC levels, related to additional adipocyte aldosterone production [48].

Follow-up in patients on medical treatment

Follow-up BP measurements and laboratory analyses should be scheduled after treatment initiation, as depicted in Fig. 3. If the dose is unchanged, MRA treated patients should be periodically tested in the first year every 3–6 months for PRA or DRC and from then on annually. The objective of the treatment is to achieve a BP < 130/80 mmHg, potassium levels >3.5 nmol/L, and normalization of plasma renin levels or the ARR while reducing other antihypertensive treatments.

The normalization / un-suppression of renin or the ARR, independently of the MRA dose used, is the only indicator reported so far to decrease cardiovascular and metabolic

events and death at long-term follow-up in medically treated PA [4, 23]. Nevertheless, in case of elevated renin levels, the MRA dose should be reduced. In addition, we should be taken into account that renin can rise because of concomitant treatment with RAS-inhibitors and/or thiazide diuretics and by contrast remain low because of concomitant betablockers administration; thus, sometimes the normalization of these parameters is difficult to evaluate.

Mild hyperkalemia is a common side effect of MRA that can be worsened by instructions to minimize salt intake. Generally accepted risk factors are old age (>60 years), impaired renal function at diagnosis, and long-term hypertension. Therefore, a cautious increase of MRA therapy and the recommendation of normalization of salt intake are indicated, except in patients with persistently suppressed renin or a pathological ARR ratio who can maintain salt restriction [49].

Ambulatory treatment of mild hyperkalemia consists of weekly monitoring of serum potassium concentrations, instruction to reduce dietary potassium content, increasing salt and fluid intake, adjusting MRA dose, and adjusting antihypertensive medication (withdrawal of other potassium-sparing medication like ACEIs or AIIRAs, starting with loop diuretics) [46].

Other follow-up considerations

As mentioned above, PA is associated with a worse metabolic and cardiovascular outcome than essential HT [50]. Therefore, a close and regular follow-up of these patients is mandatory following the latest European Society of Hypertension Guideline [51] regarding BP control and HT target tissue damage control, with emphasis also on other specific PA-associated reported metabolic comorbidities and serum potassium control. Moreover, patients with PA should be periodically screened for hypertensive-related comorbidities, as in patients with HT due to other causes, following the same recommendations as in essential HT.

Special situations in PA

PA in older patients

Current guidelines recommend the potential screening [45] of at least 50% of patients with HT, but there are no specific recommendations for older patients, the population with the highest prevalence of HT. Typically, people over 65 years of age were evaluated, but the progressive aging of the population led us to use the concept frailty. This is a clinical condition characterized by an excessive vulnerability of the individual to endogenous and exogenous stressors. This state generates a high risk of developing an adverse health-related event, so we should consider older age as a clinical condition rather than a date of birth, and reduce invasive procedures according to fragility and not simply age [52].

Aging induces changes in the renin-angiotensin-aldosterone system (RAAS) hormones' secretion and produces adrenal histological changes that need to be considered when screening for PA in this population [53, 54]. An increase in aldosterone-producing cell clusters (now denominated as micronodules) has been observed, with a thinning and reduced expression of CYP11B2 [55]. These micronodules have been identified in adrenal tissues adjacent to APA hyperplasia, as well as in tumor-free normal human adrenal glands. They have the ability to produce renin-independent aldosterone secretion, contributing along with decreased CYP11B2 to dysregulated aldosterone production [56]. In addition, a decrease in the RAAS activity has been observed, probably due to deterioration of kidney function and reduction of PRA, keeping aldosterone levels unchanged or slightly decreased. Furthermore, an older age is associated with a blunted ability to secrete aldosterone with sodium restriction and a greater sensitivity to aldosterone with salt administration [57]. All in all, an older age has been associated with higher ARR, thus, the number of false-positive results for screening may be higher, and patients may receive unnecessary confirmatory tests or AVS. In addition to this, when the screening strategy is applied to this population, it is important to consider the comorbidities they may have, such as heart failure, diabetes mellitus, and that the medications they take can affect the results of the screening and the diagnostic procedure. Furthermore, the clinician must consider that changes in medication may decompensate the patient's clinical situation.

Older and fragile patients with a "real positive ARR" could be empirically treated with an MRA or proceed to a diagnostic test depending on their basal clinical situation. If clinicians choose to proceed with diagnostic testing, they should consider the risks of volume expansion under sodium loading, the increased risk of hypokalemia in elderly patients with comorbidities, and impaired response to physiological stimuli such as saline infusion; therefore, the captopril test should be the test of choice in this population.

Regarding imaging, CT and MRI have shown poor accuracy in predicting unilateral disease, and this is even more certain in older age [58], where the prevalence of non-functioning adenoma increases. Therefore, it seems reasonable to offer AVS to otherwise healthy patients, in whom surgery could achieve a total cure from the PA, or to those patients who cannot tolerate medication or have contraindications [59]. AVS success is similar between age groups. The PASO study showed that older age is a negative predictor of clinical success but not for a biochemical one in adrenalectomized patients [13] due to the long history of HT and the already affected cardiovascular system [9]. A lateralization index greater than 4 in patients older than 65 was the best indicator to achieve complete clinical

remission. For those patients in whom surgery is not an option, MRA should be started with low doses of spironolactone (25–50 mg per day) or eplerenone. If it is not well tolerated, guidelines recommend the use of amiloride.

This population is particularly susceptible to developing renal impairment, a decline in glomerular filtration rate, and hyperkalemia after adrenalectomy and during MRA treatment, due to the reduction of plasma volume. Therefore, it is mandatory to carefully monitor these parameters promptly after surgery (24 h post-surgery) and during medical treatment.

Hyperaldosteronism and pregnancy

Pregnancy is a hyperreninemic hyperaldosteronism state, thus, the diagnosis of PA is difficult to establish during gestation, since the ARR does not apply to this population. Additionally, HT is a common complication of pregnancy (6–8% of pregnant women). If the prevalence of PA is approximately 10% in patients with hypertension, we could speculate that 0.6% of the pregnant women with hypertension have PA [60, 61].

During the first trimester, at approximately 8 weeks of gestation, PRA rises by approximately 4-fold and continues to increase up to sevenfold at term, just as aldosterone levels during pregnancy can reach levels tenfold higher than baseline. These changes are due to the additional sources of renin from the uterus, the ovaries, and the placenta, and a rise of estrogen that also stimulates renin and hence, aldosterone secretion. Moreover, progesterone acts as a competitive antagonist at the mineralocorticoid receptor, raising aldosterone levels in parallel with the changes in progesterone throughout gestation. The presence of hypokalemia could increase the probability of PA during pregnancy, but the serum potassium level may be normal due to the progesterone effect on mineraloid receptors.

Therefore, a high ARR together with suppressed PRA and consistent clinical features might be suggestive of PA. Some authors consider that a PRA below 4 ng/ml/h is suggestive of PA in pregnancy [62]. But the definitive diagnosis can only be made after delivery, since confirmation tests such as saline infusion tests or captopril tests are not recommended during pregnancy, due to risks associated with volume expansion or toxic effects [63].

The optimal management of PA during pregnancy is unclear, as most cases were published as case reports, making this a very heterogeneous population with significant differences in medical management [64, 65]. If PA is diagnosed before pregnancy as a unilateral form, adrenalectomy must be performed prior to conception [65]. If it is a medically treated bilateral disease, drugs such as spironolactone should be discontinued before pregnancy, and drugs with no risk of teratogenicity must be introduced.

When a diagnosis is made during pregnancy, the treatment approach should be antihypertensive drugs known to be safe during pregnancy. If methyldopa and/or a beta-blocker are insufficient, diuretics such as amiloride can be indicated, along with potassium supplementation if needed. If BP is still uncontrolled in the second trimester, spironolactone (FDA pregnancy category C) or eplerenone (FDA pregnancy category B) may be an option considering risk/benefits for mother and baby, but currently, no clinical guideline reports sufficient evidence [63]. The second trimester could be a good moment to perform laparoscopic adrenalectomy if unilateral PA is diagnosed. Imaging with MRI or echography is safe, and the presence of a unilateral APA in a young pregnant woman with hypertension before the 20th week of pregnancy and biochemical evidence of PA could be enough confirmation to indicate surgery.

Hyperaldosteronism and chronic kidney disease

The impact of PA on chronic kidney disease (CKD) deserves special consideration.

PA is associated with increased rates and severity of albuminuria and kidney failure progression, while CKD evolution is accompanied by an accelerated CV burden. Despite this, screening for hyperaldosteronism in CKD is performed less frequently than in the general population, especially in older patients with a lower estimated glomerular filtration rate (eGFR) and normal serum potassium, preventing some patients from benefiting from its assessment and treatment [63].

Another key point in CKD refers to MRA treatment for fear of hyperkalemia. It has been shown that in patients with CKD stages 1 to 3 treated with MRA, a minimal decrease in eGFR and increase in serum potassium (-5.4 ± 1.9 ml/min/1,73m2 and 0.3 ± 0.1 mmol/l, respectively) were observed at 3 months and maintained at 12 months of follow-up. The drug discontinuation rate due to these changes was 3.29%. Moreover, CKD patients treated with dialysis administered MRA presented an improved clinical outcome with reduced cardiovascular mortality. Regular screening and treatment of PA is, therefore, mandatory in CKD patients [63].

Conclusions

Primary aldosteronism is the most frequent cause of secondary hypertension and is associated with a higher cardiometabolic risk than essential hypertension. MRA and surgical treatment are effective in controlling BP and reducing associated cardiovascular risk. The new pathological classification (HISTALDO) may be useful in predicting the risk of recurrence after unilateral resection. Clinical and biochemical follow-up should be systematically performed and adapted according to the type of treatment applied to control PA (medical or surgical) and PA associated comorbidities.

Acknowledgements We thank Alberto Fernandez for the review of the manuscript. This consensus was sponsored by all implicated Societies.

Author contributions "MAC and FH wrote the main manuscript text and all authors reviewed the manuscript."

Funding This research was funded by all implicated societies.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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