

Consensus

**SFE/SFHTA/AFCE primary aldosteronism consensus:
Introduction and handbook**

Consensus sur l'hyperaldostéronisme primaire de la SFE/SFHTA/AFCE : introduction et guide

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Abstract

The French Endocrinology Society (SFE) French Hypertension Society (SFHTA) and Francophone Endocrine Surgery Association (AFCE) have drawn up recommendations for the management of primary aldosteronism (PA), based on an analysis of the literature by 27 experts in 7 work-groups. PA is suspected in case of hypertension associated with one of the following characteristics: severity, resistance, associated hypokalemia, disproportionate target organ lesions, or adrenal incidentaloma with hypertension or hypokalemia. Diagnosis is founded on aldosterone/renin ratio (ARR) measured under standardized conditions. Diagnostic thresholds are expressed according to the measurement units employed. Diagnosis is established for suprathreshold ARR associated with aldosterone concentrations > 550 pmol/L (200 pg/mL) on 2 measurements, and rejected for aldosterone concentration < 240 pmol/L (90 pg/mL) and/or subthreshold ARR. The diagnostic threshold applied is different if certain medication cannot be interrupted. In intermediate situations, dynamic testing is performed. Genetic forms of PA are screened for in young subjects and/or in case of familial history. The patient should be informed of the results expected from medical and surgical treatment of PA before exploration for lateralization is proposed. Lateralization is explored by adrenal vein sampling (AVS), except in patients under 35 years of age with unilateral adenoma on imaging. If PA proves to be lateralized, unilateral adrenalectomy may be performed, with adaptation of medical treatment pre- and postoperatively. If PA is non-lateralized or the patient refuses surgery, spironolactone is administered as first-line treatment, replaced by amiloride, eplerenone or calcium-channel blockers if insufficiently effective or poorly tolerated.

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Keywords: Consensus; Primary aldosteronism; Hypokalemia; Resistant hypertension; Severe hypertension; Adrenal incidentaloma

Résumé

La SFE, la SFHTA et l'AFCE ont élaboré des recommandations sur la prise en charge de l'hyperaldostéronisme primaire (HAP), à partir d'une analyse de la littérature par 27 experts formant 7 groupes de travail. Un HAP est recherché devant une hypertension artérielle (HTA) présentant une des caractéristiques suivantes : sévère ; résistante ; associée à une hypokaliémie ; associée à un retentissement disproportionné sur les organes cibles, et devant un incidentalome surrénalien avec HTA ou hypokaliémie. Le diagnostic repose sur le rapport aldostérone/rénine (RAR) mesuré en conditions standardisées. L'expression du seuil diagnostique (SD) dépend des unités de mesure. Lorsque le RAR est $> SD$ et l'aldostérone > 550 pmol/L (> 200 pg/mL) à 2 reprises, le diagnostic est affirmé, si aldostérone < 240 pmol/L (< 90 pg/mL) ou RAR $< SD$ il est rejeté. Un SD différent est utilisé si certains médicaments ne peuvent être arrêtés. Dans les situations intermédiaires, un test dynamique est réalisé. Une forme génétique d'HAP est recherchée chez le sujet jeune et/ou en présence d'histoire familiale. Une information sur les résultats des traitements médicaux et chirurgicaux de l'HAP doit être donnée au patient avant de proposer la recherche d'une latéralisation. Celle-ci repose sur le cathétérisme des veines surrénaliennes (CVS), sauf patients < 35 ans avec image d'adénome unilatéral. Si l'HAP est latéralisé, une surrénalectomie unilatérale peut être proposée, elle est encadrée d'adaptations du traitement médical. Si l'HAP n'est pas latéralisé ou si le patient refuse la chirurgie la spironolactone est utilisée en première intention, amiloride, éplérenone, et inhibiteurs calciques sont utilisés si elle est insuffisamment efficace ou mal tolérée.

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Mots clés : Consensus ; Hyperaldostéronisme ; Hypokaliémie ; Hypertension résistante ; Hypertension sévère ; Incidentalome surrénalien

1. Introduction

Primary aldosteronism (PA) is one of the most frequent causes of secondary hypertension. Untreated hypertension aggravates cardiovascular morbidity beyond what could be expected from blood-pressure level alone. Prevention requires screening for hypertensive patients, to enable specific medical or surgical management. The present consensus statement formulates a therapeutic and diagnostic guide for physicians dealing with hypertensive patients.

The French Endocrinology Society (SFE), in collaboration with the French Hypertension Society (SFHTA) and Francophone Endocrine Surgery Association (AFCE), undertook a consensus statement on hypertension management, bringing together a group of 27 French-speaking experts in

the various specialties concerned: endocrinology, cardiology, nephrology, endocrine surgery, internal medicine, genetics, radiology, nuclear medicine, plus one methodologist.

The experts were divided into 7 work-groups on the following topics: epidemiology; initial diagnostic steps, diagnostic confirmation, etiologic diagnosis, genetic forms, surgical treatment, and medical treatment. Each group was entrusted with drawing up recommendations based on analysis of the significant scientific studies published in the previous 20 years, and reporting this literature analysis in a review article. Evaluation of recommendation strength and level of evidence was to be based on the GRADE method.

Three plenary sessions were held in the premises of the SFE and SFHTA in Paris in 2013, and were followed up by numerous exchanges within and between groups via the Internet. The texts

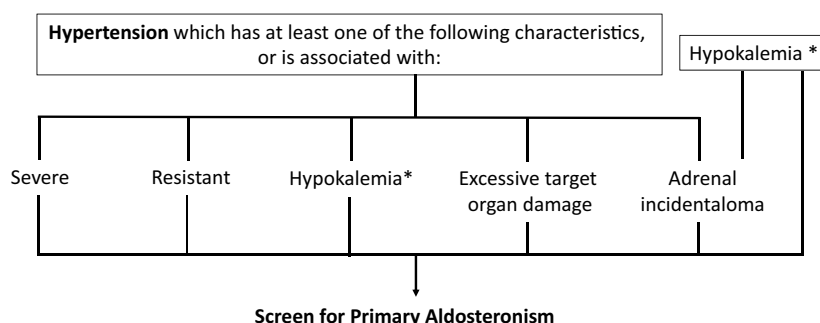


Fig. 1. Clinical associations that justify screening for primary aldosteronism. * Hypokalemia without obvious digestive loss of potassium.

of the recommendations made by each group were assessed and revised by the whole expert group. An oral presentation of the work was made to the SFE Congress in Paris on October 6, 2013 and to the SFHTA Congress in Paris on December 20, 2013.

Writing up the recommendations and articles continued through to 2015, taking on board significant contributions published since 2013. The texts of the 47 recommendations and 7 review articles underwent internal review before publication.

The Handbook presented below is intended to allow a quick reading of the consensus. It comprises the abstracts of each review article, an abridged version of the corresponding recommendations, and illustrative figures, concluding with pointers toward future perspectives. To fully appreciate the rationale underlying the recommendations, however, close reading of the actual review articles remains indispensable.

2. Handbook

2.1. Epidemiology of primary aldosteronism: who should be screened for sporadic PA? [1]

Depending on the study, the prevalence of primary aldosteronism (PA) in patients with hypertension varies from 6 to 18% (Fig. 1, Table 1).

Prevalence is higher in each of the following conditions, any one of which requires screening for PA:

- severe hypertension (systolic blood pressure (BP) ≥ 180 mmHg or diastolic BP ≥ 110 mmHg);

- resistant hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg despite at least three antihypertensive drugs including a thiazide diuretic);
- hypertension associated with hypokalemia (either spontaneous or associated with a diuretic);
- hypertension or hypokalemia associated with adrenal incidentaloma.

It should be borne in mind that PA can induce hypertension without hypokalemia or, less frequently, hypokalemia without hypertension.

Finally, as cardiovascular and renal morbidity is greater in PA than in essential hypertension of equivalent level, screening for PA is indicated when cardiovascular or renal morbidity is more severe than expected from blood pressure levels.

2.2. First diagnostic steps [2] and confirmatory testing [3]

In patients with suspected primary aldosteronism (PA), the first diagnostic step, screening, must have high sensitivity and negative predictive value (Fig. 2, Table 2, Table 3). The aldosterone-to-renin ratio (ARR) is used because it has higher sensitivity and lower variability than other measures (serum potassium, plasma aldosterone, urinary aldosterone). ARR is calculated from the plasma aldosterone (PA) and plasma renin activity (PRA) or direct plasma renin (DR) values.

These measurements must be taken under standardized conditions: in the morning, more than 2 hours after awakening, in sitting position after 5 to 15 minutes, with normal

Table 1
Abbreviated recommendations on screening for Primary Aldosteronism [1].

N°	Recommendations on screening for PA	Strength	Evidence
1.1	Severe hypertension ^a Grade 3, Systolic BP ≥ 180 mmHg and/or Diastolic BP ≥ 110 mmHg	Strong	++
1.2	Resistant hypertension ^a BP $\geq 140/90$ mmHg despite lifestyle modifications and at least 3 antihypertensive drugs including 1 thiazide diuretic (or loop diuretic if renal insufficiency)	Strong	++
1.3	Hypertension and hypokalemia Plasma potassium (< 3.5 mmol/L), whether spontaneous or diuretic-induced, without obvious digestive potassium losses	Strong	++
1.5	Adrenal incidentaloma with hypertension and/or hypokalemia	Strong	++
1.6	Hypertension with disproportionate target organs damage ^b	Weak	+

^a 1.4. Even if kalemia is normal.

^b 1.7. Given the absence of therapeutic impact, indications for target organ lesion screening are the same in PA as in the general population of hypertensive patients.

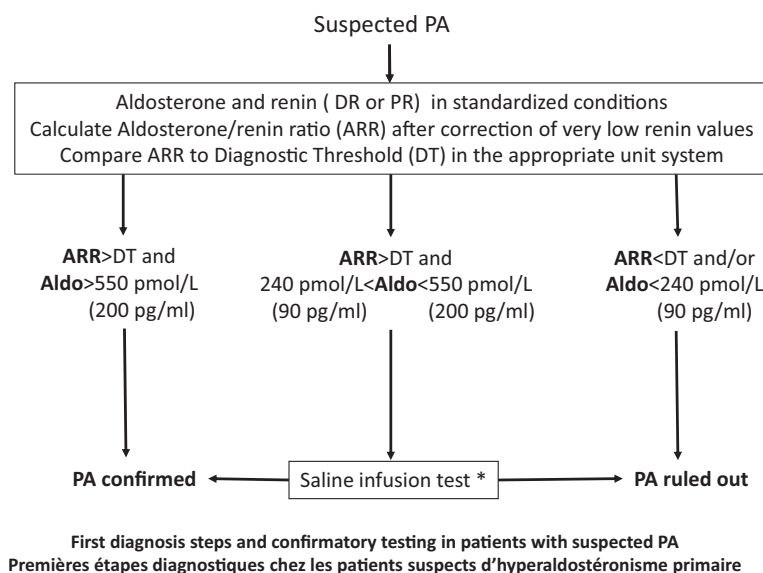


Fig. 2. First diagnosis steps and confirmatory testing in patients with suspected PA. *If saline infusion test is contraindicated by cardiac insufficiency, captopril test is proposed.

dietary salt intake, normal serum potassium level and without antihypertensive drugs significantly interfering with the renin-angiotensin-aldosterone system (see footnotes in Table 1 of [2]). Antihypertensive drugs that can be maintained during exploration include alpha-blockers and calcium channel blockers (ideally long-acting and non-dihydropyridine antagonists).

To rule out ARR elevation due to very low renin values, ARR screening is applied only if aldosterone is > 240 pmol/L (90 pg/mL); DR values < 5 mIU/L are set to a minimum of 5 mIU/L and PRA values < 0.2 ng/mL/h to 0.2 ng/mL/h. We propose threshold ARR values depending on the units used and the conversion factor (pg to mIU) for DR (Table 2).

- if ARR is below threshold and/or if plasma aldosterone is < 240 pmol/L (90 pg/mL) on two measurements, diagnosis of PA is excluded;
- if ARR exceeds threshold, PA should be suspected and exploration continued. In patients with elevated ARR and plasma aldosterone concentration above 550 pmol/L (200 pg/mL) on two assessments, PA can be diagnosed without confirmatory testing;
- in patients not corresponding to either of the previous conditions, dynamic confirmatory testing is mandatory. Several tests are available based on aldosterone suppression by saline loading, fludrocortisone administration or converting enzyme inhibition by captopril. One test is based on renin stimulation

Table 2

Minimum ARR thresholds for considering primary aldosteronism in a patient explored in standard conditions, expressed in different unit systems and with direct renin set at a minimum of 5 mIU/L and PRA at a minimum of 0.2 ng/mL/h.

Renin Aldosterone	Direct renin (mIU/L)	Direct renin (pg/mL) 1 pg/mL = C mIU/L	Plasma renin activity (ng/mL/h)	Plasma renin activity (pmol/L/mn)
pmol/L	64	64 × C	830	70
pg/mL (= ng/L)	23	23 × C	300	25

Table 3

Abbreviated recommendations on first steps [2] and confirmatory testing [3].

N°	Recommendation on first steps for diagnosis of PA	Strength	Evidence
R2.1	Measurement of Aldosterone/renin ratio (ARR) in standardized conditions	Strong	++
R2.2	Threshold values of ARR expressed in different unit systems (Table 2)	Strong	++
R2.3R3.3	ARR < threshold and/or Aldo < 240 pmol/L (90 pg/mL). PA excluded	Strong	++
R3.4	ARR > threshold and Aldo > 550 pmol/L (200 pg/mL). PA confirmed	Strong	++
R3.5	ARR > threshold and 550 pmol/L (200 pg/mL) > Aldo > 240 pmol/L (90 pg/mL) PA can neither be excluded or confirmed. A dynamic test is necessary	Weak	++
R3.6	Dynamic testing: Intravenous sodium load. If cardiac function does not allow intravenous sodium load, perform a captopril test	Weak	++

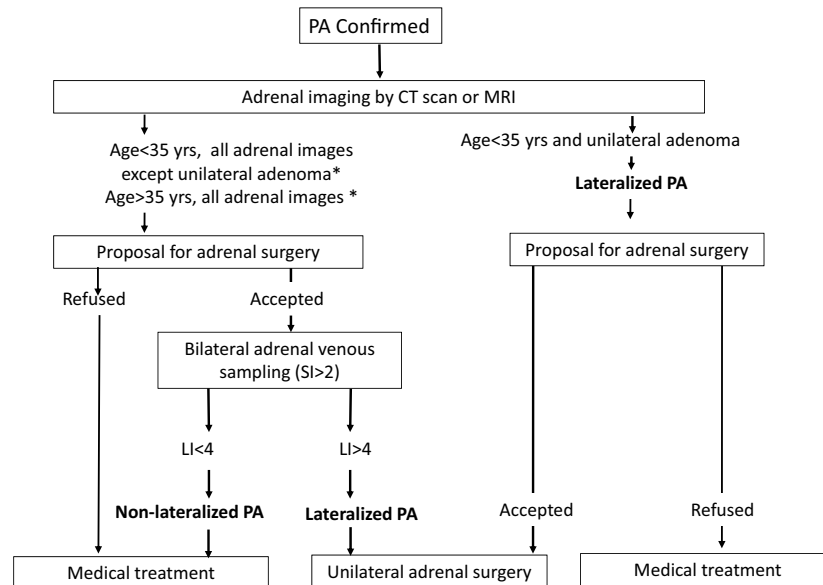


Fig. 3. Subtype diagnosis. *Including images of bilateral adenoma, bilateral hyperplasia or normal adrenals. LI: lateralization index; SI: selectivity index.

by furosemide administration. Each of these tests has its limitations, and validation is incomplete. We recommend aldosterone suppression by saline load. Renin stimulation by captopril may be used if sodium loading is contraindicated by excessively impaired cardiac function.

2.3. Subtype diagnosis of PA [4]

To establish the cause of primary aldosteronism (PA), it is essential to distinguish unilateral from bilateral adrenal aldosterone secretion, as adrenalectomy improves aldosterone secretion and controls hypertension and hypokalemia only in the former (Fig. 3, Table 4).

Except in the rare cases of type 1 or 3 familial hyperaldosteronism, which can be diagnosed genetically, lateralized aldosterone secretion is diagnosed on adrenal CT or MRI and adrenal venous sampling.

Postural stimulation tests and ^{131}I -norcholesterol scintigraphy have poor diagnostic value and ^{11}C -metomidate PET is not yet available.

We recommend that adrenal CT or MRI be performed in all cases of PA. Imaging may exceptionally identify adrenocortical carcinoma, for which the surgical objectives are carcinologic, and otherwise shows either normal or hyperplastic adrenal glands or unilateral adenoma.

Imaging alone carries a risk of false positives in patients over 35 years of age (non-aldosterone-secreting adenoma) and false negatives in all patients (unilateral hyperplasia).

We suggest that all candidates for surgery over 35 years of age undergo adrenal venous sampling, simultaneously in both adrenal veins, without ACTH stimulation, to confirm the unilateral form of the hypersecretion.

Sampling results should be confirmed on adrenal vein cortisol assay showing a concentration at least double that found in peripheral veins.

Table 4
Abbreviated Recommendations on subtype diagnosis of PA [4].

N°	Recommendations	Strength	Evidence
R4.1	Imaging by CT scan or MRI In all patients with confirmed PA	Weak	+
R4.2	Adrenal venous sampling (AVS), indications: do not perform AVS in patients who are not candidates for surgery	Strong	++
R4.4	Adrenal venous sampling, indications: perform AVS in all patients above 35 yrs who are candidates for surgery (except rare patients with malignant adrenal tumor on imaging)	Strong	++
R4.3	Adrenal venous sampling, implementation: bilateral catheterization of both adrenal veins, with no ACTH stimulation Selectivity Index ≥ 2 Lateralization Index ≥ 4	Strong	++
R4.5	Functional imaging not indicated	Weak	+
R4.6	Posture test not indicated	Weak	+

Table 5
Abbreviated Recommendations on genetic diagnosis of PA [5].

N°	Recommendations on diagnosis of genetic forms of PA	Strength	Evidence
R5.1.1	Search for FH-I if PA before 20 yrs of age or PA and familial history of PA or PA and familial history of stroke before 40 yrs of age	Strong	++
R5.1.2	Diagnosis of FH-I: search for hybrid gene <i>CYP11B1/B2</i> by long-range PCR or Southern	Strong	++++
R5.1.3	Blot		
R5.2.1	Search for FH-III if PA before 20 yrs of age or resistant hypertension with hypokalemia before 20 yrs of age or familial history of PA before 20 yrs of age	Strong	++
R5.2.2	Diagnosis of FH-III: exclusion of chimeric <i>Cyp11B1/B2</i> gene	Strong	++++
R5.2.3	Sequencing of <i>KCNJ5</i> gene (exon 2, coding for the region carrying the recurrent mutations found in PA)		
R5.3.1	Search for FH-II if hypertension with familial history of confirmed PA	Weak	+
R5.3.2	Diagnosis of FH-II: confirmation of PA and exclusion of FH-I and FH-III (on genetic testing)	Weak	++
R5.4.1	A genetic disease associating PA, seizures and neurologic abnormalities should be screened for in children with the following criterion: early hypertension and PA in the context of complex neurologic syndrome with seizures	Weak	+
R5.4.2	Genetic screening seeks to detect recurrent mutation of <i>CACNA1D</i> gene, and should use <i>CACNA1D</i> gene sequencing	Strong	++
R5.5.1	Search for FH-IV if early hypertension and PA before the age of 10 years	Weak	+
R5.5.2	Diagnosis of FH-IV: <i>CACNA1H</i> gene sequencing	Strong	++

Aldosterone secretion should be considered lateralized when aldosterone/cortisol ratio on the dominant side is at least 4-fold higher than contralaterally.

2.4. Genetic diagnosis of PA [5]

While the majority of cases of primary aldosteronism (PA) are sporadic, four forms of autosomal-dominant inheritance have been described: familial hyperaldosteronism (FH) types I to IV (Table 5):

- FH-I, also called glucocorticoid-remediable aldosteronism, is characterized by early and severe hypertension, usually before the age of 20 years. It is due to the formation of a chimeric gene between the adjacent *CYP11B2* and *CYP11B1* genes (coding for aldosterone synthase and 11 β -hydroxylase, respectively). FH-I is often associated with family history of stroke before 40 years of age;
- FH-II is clinically and biochemically indistinguishable from sporadic forms of PA and is only diagnosed on the basis of two or more affected family members. No causal genes have been identified so far and no genetic test is available;
- FH-III is characterized by severe and early-onset hypertension in children and young adults, resistant to treatment and associated with severe hypokalemia. Mild forms, resembling FH-II, have been described. FH-III is due to gain-of-function mutations in the *KCNJ5* gene;
- recently, a new autosomal-dominant form of familial PA, FH-IV, associated with mutations in the *CACNA1H* gene, was described in patients with hypertension and PA before the age of 10 years.

In rare cases, PA may be associated with complex neurologic disorder involving epileptic seizures and cerebral palsy (Primary

aldosteronism, seizures and neurologic abnormalities [PASNA]) due to *de novo* germline *CACNA1D* mutations.

2.5. Adrenal surgery in PA [6]

Treatment of primary aldosteronism (PA) aims at preventing or correcting hypertension, hypokalemia and target organ damage (Fig. 3, Table 6).

Patients with lateralized PA and candidates for surgery may be managed by laparoscopic adrenalectomy. Partial adrenalectomy and non-surgical ablation have no proven advantage over total adrenalectomy. Intraoperative morbidity and mortality are low in reference centers, and day-surgery is warranted in selected cases.

Spironolactone administered during the weeks preceding surgery controls hypertension and hypokalemia and may prevent postoperative hypoaldosteronism.

In most cases, surgery corrects hypokalemia, improves control of hypertension and reduces the burden of pharmacologic treatment; in about 40% of cases, it resolves hypertension.

However, success in controlling hypertension and reversing target organ damage seems comparable with mineralocorticoid receptor antagonists. Informed patient preference with regard to surgery is thus an important factor in therapeutic decision-making.

2.6. Medical treatment of primary aldosteronism [7]

First-line medical treatment of primary aldosteronism (PA) is spironolactone, a mineralocorticoid receptor antagonist. As it is also an androgen and progesterone receptor antagonist, it incurs adverse effects, especially in males (Fig. 3, Table 7).

In case of spironolactone intolerance, amiloride provides good control of hypokalemia, and we suggest that eplerenone,

Table 6

Abbreviated Recommendations on adrenal surgery [6].

N°	Recommendations	Strength	Evidence
R6.11	Treatment decision only after patients' information on following points: -Adrenal nodule is benign -Medical and surgical treatment of PA seem to have comparable results -Medical treatment of PA is not always well tolerated, and must be life-long -If unilateral PA, surgery possible at any time -Surgery generally allows terminating some drugs, but postoperative antihypertensive treatment is needed in more than half of cases	Strong	+
R6.12	Treatment decision should be discussed prior to adrenal vein sampling; medical trial period possible	Strong	+
R6.1	Laparoscopic rather than open surgery	Strong	+++
R6.2	Trans- or retro-peritoneal approach, with or without robot-assistance, according to patient's profile and surgeon's preferences	Strong	+
R6.3	Except in special cases, unilateral total adrenalectomy	Weak	+
R6.4	Experimented surgeon in a reference center	Weak	+
R6.5	In reference centers, selected patients on an outpatient basis	Weak	++
R6.6	Preoperative mineralocorticoid receptor antagonist \pm potassium treatment	Strong	+
R6.7	Mineralocorticoid receptor antagonists, potassium, low salt diet and antihypertensive drugs stopped just before surgery	Strong	+
R6.8	Postoperative monitoring of blood pressure and kalemia. Antihypertensive treatment resumed if postoperative hypertension. Fludrocortisone initiated if persistent symptomatic hyperkalemia or persistent hypotension	Strong	+
R6.9	Postoperative hormone analysis recommended if persistent hypertension or hypokalemia, and suggested in case of clinical and biological cure of PA	Strong Weak	+
R6.10	Cessation of follow-up if normal blood pressure and kalemia at 1 year without treatment. Appropriate follow-up if persistent hypertension or persistent PA	Strong	+

Table 7

Abbreviated recommendations on medical treatment of PA [7].

N°	Recommendations	Strength	Evidence
R7.1	Spironolactone treatment in non-lateralized PA, and in lateralized PA for patients not wishing or unable to undergo surgery	Strong	+++
R7.2	If spironolactone intolerance, amiloride as replacement or with low-dose spironolactone	Strong	++
R7.3	In case of non-controlled hypokalemia with spironolactone intolerance, amiloride preferred to potassium supplementation	Strong	+
R7.4	Eplerenone in case of spironolactone intolerance and amiloride ineffectiveness	Strong	+
R7.5	In second or third line, calcium channel blockers or thiazide diuretics	Weak	+

a more selective but less powerful mineralocorticoid receptor antagonist, may be used in case of spironolactone intolerance and/or insufficient control of hypertension by amiloride.

Specific calcium channel blockers and thiazide diuretics may be used as second or third line therapy.

Medical treatment of bilateral forms of PA seems to be as efficient as surgical treatment of lateralized PA for the control of hypertension and prevention of cardiovascular and renal morbidity.

Thus, medical treatment may be proposed to patients with lateralized forms of PA who refuse surgery or to PA patients who refuse adrenal venous sampling to determine whether they have bilateral or lateralized PA.

2.7. Perspectives

To achieve the present consensus, we had first to determine the state of the art in clinical research in hypertension. This, of course, also entailed identifying the gaps. We therefore detail

below a few issues remaining to be fully resolved, and the corresponding needs and perspectives. The list is undoubtedly incomplete and piecemeal, but we hope it will help stimulate further research.

- Difficulties in positive diagnosis: contribution of urinary aldosterone assay by mass spectrometry?
- Invasiveness of etiological diagnosis: promising developments in functional imaging, notably by metomidate scintigraphy ([¹¹¹C]metomidate, as used in PET, and [¹²³I]iodometomidate); and progress in genetics and biomimetics, enabling new genetic abnormalities to be identified in familial and sporadic forms, and new circulating molecular markers to be developed.
- Treatment assessment: studies to allow more rigorous comparison of efficacy between medical and surgical management of lateralized forms, especially regarding prevention of cardiovascular and renal morbidity in PA, improved prediction of benefit with surgery, and standardization of the definition of

post-treatment improvement in blood pressure in lateralized PA; and precise assessment of the benefit of non-operative treatments of lateralized PA, so as to determine their role in treatment strategy.

Disclosure of interest

The authors declare that they have no competing interest.

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