PRIMARY ALDOSTERONISM

CHI Formulary Development Project

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October 2023

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Abbreviations

ACE	Angiotensin I-Converting Enzyme
ACTH	Adrenocorticotrophic Hormone
AFCE	Francophone Endocrine Surgery Association
APAs	Aldosterone-Producing Adenomas
ARR	Aldosterone-to-Renin Ratio
AVS	Adrenal Venous Sampling
BAH	Bilateral Adrenal Hyperplasia
BP	Blood Pressure
CHI	Council of Health Insurance
CT	Computerized Tomography
DR	Direct Renin
FH	Familial Hyperaldosteronism
FH-I	FH Type I
FH-II	FH Type II
FH-III	FH Type III
FH-IV	FH Type IV
GRA	Glucocorticoid-Remediable Aldosteronism
IDF	CHI Drug Formulary
IHA	Idiopathic Hyperplasia
MRAs	Mineralocorticoid Receptor Antagonists
MRI	Magnetic Resonance Imaging
PA	Primary aldosteronism
PASNA	PA, Seizures, and Neurologic Abnormalities
PRA	Plasma Renin Activity
RAAS	Renin-Angiotensin-Aldosterone System
SFDA	Saudi Food and Drug Authority
SFE	French Endocrinology Society
SFHTA	French Hypertension Society
UAH	Unilateral Adrenal Hyperplasia

Executive Summary

The Renin-Angiotensin-Aldosterone System (RAAS) plays a critical role in maintaining the body's balance of sodium, blood volume, and Blood Pressure (BP). This system operates in a hierarchical manner, beginning with the production of renin by kidney cells known as juxtaglomerular cells. Renin release is triggered by factors such as reduced kidney blood flow, low sodium levels in the renal tubules, and activation of the sympathetic nervous system through central ß1 adrenergic receptors. Renin's main function is to control the rate-limiting step of the RAAS by converting angiotensinogen into angiotensin I. This inactive form is then activated into the vasopressor octapeptide angiotensin II by Angiotensin I-Converting Enzyme (ACE) in the endothelium of the lung and kidney. Angiotensin II, in turn, stimulates the release of aldosterone from the outer layer of the adrenal cortex, known as the zona glomerulosa. This hormone acts on the nephrons in the kidneys to increase the reabsorption of sodium and water. Figure 1 illustrates the RAAS, a crucial physiological pathway in the regulation of BP and fluid balance[1].

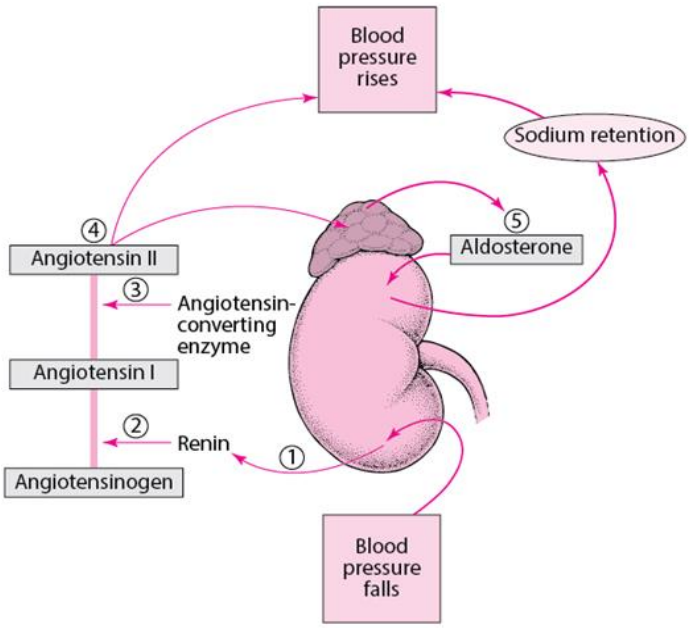

Figure 1. *The Renin-Angiotensin-Aldosterone System*

Primary aldosteronism (PA), first described by Jerome Conn in 1954, is characterized by excessive production of aldosterone, independent of the usual triggers of renin and angiotensin II. This excess aldosterone leads to increased reabsorption of sodium in the renal tubules and an expansion of blood volume, resulting in hypertension and hypokalemia. PA causes suppression of renin secretion due to the increased delivery of sodium chloride to the juxtaglomerular apparatus. As a result,

the Aldosterone-to-Renin Ratio (ARR) is elevated, indicating inappropriate aldosterone levels for the blood volume and BP. Apart from raising blood pressure, excess aldosterone is associated with an increased risk of cardiovascular problems and mortality[2].

PA, once considered rare, is a heterogeneous group of disorders caused by the autonomous overproduction of aldosterone with simultaneous suppression of plasma renin activity. It is considered to be the most common endocrine cause of secondary arterial hypertension and is associated with a high rate of cardiovascular complications, such as increase in left ventricular mass measurements, stroke, myocardial infarction, heart failure, and atrial fibrillation. The introduction of the ARR as a screening test and its application to a broader population of hypertensive individuals has significantly increased the detection of PA. This increase is especially notable among patients with normal potassium levels. Most research groups have reported PA prevalence rates ranging from 5% to 15%, with most patients having normal potassium levels. In groups of patients with resistant hypertension, the prevalence rates have approached 20% or even higher. High prevalence rates of PA have also been observed among hypertensive patients with atrial fibrillation or diabetes mellitus[3].

Progress in molecular histopathology challenges the conventional understanding of PA as a binary condition, where unilateral Aldosterone-Producing Adenomas (APAs) are contrasted with Bilateral Adrenal Hyperplasia (BAH). Consequently, many subtypes of PA have been described since Conn's original report of the APAs in 1954. The most common forms of PA (60 to 70 percent) include bilateral idiopathic hyperaldosteronism or Idiopathic Hyperplasia (IHA), and Unilateral APAs (≥10 mm) or aldosterone-producing micronodules (<10 mm; 30 to 40 percent). The autonomous production of aldosterone in most adenomas is driven by somatic mutations. These same mutations have been detected in nodular lesions adjacent to APAs and in patients with bilateral disease and are responsible for the independent production of aldosterone. Additionally, rarer causes of PA include genetic disorders of steroidogenesis (Familial Hyperaldosteronism (FH) type I, II, III and IV), aldosterone-producing adrenocortical carcinoma, and ectopic aldosterone-producing tumors. Genetic testing for inherited forms of FH makes it easier to diagnose positive patients and avoids the complicated diagnostic steps[4].

FH is a rare underlying cause of PA. FH type I (FH-I) or Glucocorticoid-Remediable Aldosteronism (GRA) is inherited in an autosomal dominant manner and accounts for 1% of PA cases. It often has a positive family history, and an early cerebral hemorrhage can be a related complication. FH-I is the result of genetic recombination errors between the CYP11B1 gene (responsible for cortisol synthesis) and the CYP11B2 gene (responsible for aldosterone synthesis). This genetic mishap leads to the excessive production of aldosterone and hybrid steroids (18-

hydroxycortisol and 18-oxocortisol) under the control of Adrenocorticotrophic Hormone (ACTH) in the zona fasciculata. FH type II (FH-II) is an autosomal dominant disorder and is more common than FH-I (accounts for at least 7% of PA cases). FH-II is caused by germline *CLCN2* pathogenic variants. CLCN2 is a gene encoding the chloride channel and its mutation results in increased chloride efflux from glomerulosa cells, leading to depolarization, calcium influx through voltage-gated calcium channels, and elevated aldosterone production. FH type III (FH-III) includes individuals with germline mutations in the KCNJ5 gene, which codes for an inward rectifier potassium channel. These mutations cause abnormal sodium permeability of the channel, leading to cell depolarization and activation of the calcium pathway followed by increased aldosterone production and cell proliferation. Different mutations are associated with varying disease severities; some result in extensive bilateral hyperplasia and necessitate bilateral adrenalectomy, while others respond to treatment with Mineralocorticoid Receptor Antagonists (MRAs). FH type IV (FH-IV) is associated with mutations in the gene known as CACNA1H, which encodes a calcium channel protein called Cav3.2. These mutations disrupt the normal functioning of calcium channels in the adrenal glands, leading to an abnormal increase in the production of aldosterone. Finally, there is a complex syndrome known as PA, Seizures, and Neurologic Abnormalities (PASNA), which is associated with de novo germline gain-of-function mutations in the CACNA1D gene, responsible for an L-type calcium channel. This syndrome can present with symptoms like epilepsy, autism, hypoglycemia, and heart defects alongside PA[5].

The primary objective in treating patients with PA is to mitigate the associated risks of hypertension, hypokalemia, renal damage, and cardiovascular complications, thereby improving overall morbidity and mortality outcomes. Consequently, the treatment goals for PA, whether caused by unilateral or bilateral adrenal disease, remain consistent, encompassing the following key objectives: reversing the adverse cardiovascular effects of hyperaldosteronism, normalizing serum potassium levels in patients with hypokalemia, and achieving blood pressure normalization. Accurate subtype diagnosis is crucial since the treatment approach for PA is contingent upon its underlying cause. For patients with unilateral disease, such as APAs, aldosterone-producing nodules, or unilateral hyperplasia, laparoscopic adrenalectomy is recommended and represents a curative option. However, MRAs such as Spironolactone as the primary choice, with eplerenone as a secondary option, can be an alternative therapy for those who are ineligible for surgery or choose not to undergo it. Conversely, in cases of IHA or specific genetic disorders (such as GRA, FH-III, and IV), MRA therapy is suggested. In situations where patients exhibit intolerance to both spironolactone and eplerenone, amiloride or triamterene (potassium-sparing diuretics) may be considered as an alternative. In GRA cases, we recommend starting with a low-dose glucocorticoid (dexamethasone or prednisone)

to lower ACTH levels and normalize blood pressure and potassium. If blood pressure doesn't normalize, consider adding MRAs.

This report compiles all clinical and economic evidence related to PA according to the relevant sources. The ultimate objective of issuing PA guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to PA patients in Saudi Arabia. The main focus of the review was on Saudi, American, European and International guidelines issued within the last five years.

Several classes and drugs can be used for the management of PA and are summarized in the table below.

Table 1. Summary of the Recommended Medical Therapy for Primary Aldosteronism

Drug	Indication	Dose	Level of evidence
Mineralocorticoid Receptor Antagonists (MRAs)			
Spironolactone	**Unilateral Disease:** In cases where a patient is either unable or unwilling to undergo surgical intervention, Spironolactone is considered as a **secondary option**. **Bilateral Disease:** For individuals with PA caused by bilateral adrenal disease as a **first choice.**	50 to 400mg daily	1I⊕⊕○○
Eplerenone	**Unilateral Disease:** In cases where a patient is either unable or unwilling to undergo surgical intervention, Eplerenone is considered as a **secondary option**. **Bilateral Disease:** For individuals with PA caused by bilateral adrenal disease and **who do not tolerate Spironolactone**.	50 to 300mg daily, in divided doses	1I⊕⊕○○
Potassium Sparing Diuretics			

Amiloride	When **spironolactone intolerance occurs**, amiloride or triamterene can serve as **alternative treatments**, either **on their own or in conjunction with low-dose spironolactone** effectively addressing both hypertension and hypokalemia in PA patients.	10 to 40mg daily	1⊕⊕○○
Triamterene		50 to 100 mg once daily	
Corticosteroids			
Dexamethasone	Lowest effective dose, **alone or in combination with MRAs** to suppress pituitary ACTH secretion and subsequently normalize BP and potassium levels **in patients with GRA**.	0.125 mg to 0.25 mg daily at bedtime	1⊕⊕○○
Prednisone		2.5 to 7.5mg daily at bedtime	
Fludrocortisone	For **adrenalectomized patients** with persistent hypoaldosteronism, specifically **persistent hyperkalemia** necessitating **mineralocorticoid replacement therapy**.	**Starting dose:** 0.05 to 0.1 mg once daily in the morning **Maintenance dose:** 0.05 to 0.2 mg daily	Strong, evidence +

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, specific guidelines for the diagnosis and management of PA in Saudi Arabia have not been published. However, it has been discussed in the Saudi Hypertension Management Guidelines[6].

About 10% of cases of hypertension are attributed to secondary causes, including Reno parenchymal, renovascular disease, PA, Cushing syndrome, pheochromocytoma, thyroid or parathyroid disease.

PA is typically characterized by symptoms such as muscle weakness, a family history of early-onset hypertension, and cerebrovascular events occurring before the age of 40 years. In severe cases of hypokalemia, arrhythmias can be prominent during physical examination. The initial diagnostic test of choice should be measuring the ARR under standardized conditions. Additional confirmatory tests include adrenal CT scans, oral sodium loading and adrenal vein sampling.

In the **2023 Saudi Heart Association guidelines for heart failure,** resistant hypertension was defined as a seated office blood pressure exceeding 140/90 mm Hg in individuals receiving treatment with three or more antihypertensive medications at optimal or maximum tolerated doses, including a diuretic. When there is suspicion of treatment resistance, it is recommended to screen for secondary causes of hypertension, such as PA[7].

1.2 European Guidelines

1.2.1 SFE/SFHTA/AFCE Primary Aldosteronism Consensus (2016)

The French Endocrinology Society (SFE), the French Hypertension Society (SFHTA) and Francophone Endocrine Surgery Association (AFCE) have drawn up recommendations for the management of PA, based on the analysis of the literature by 27 experts in 7 workgroups[8].

1.2.1.1 Screening

The prevalence of PA in patients with hypertension varies from 6 to 18%. It is higher in each of the following conditions, any one of which requires screening for PA:

- Severe hypertension (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.

1.2.1.2 Diagnosis

In patients suspected of having PA, the initial diagnostic phase should prioritize high sensitivity and negative predictive value.

Aldosterone-to-renin ratio (ARR)

ARR is preferred due to its higher sensitivity and lower variability when compared to other measures. It is calculated using plasma aldosterone and either Plasma Renin Activity (PRA) or Direct plasma Renin (DR) values.

The measurements should adhere to standardized conditions, including collection in the morning, at least two hours after waking, in a seated position following a 5 to 15-minute rest, with normal physiological parameters, with normal dietary salt intake, normal serum potassium level and with antihypertensive that can be maintained during the exploration (alpha-blockers and calcium channel blockers).

To rule out ARR elevation due to very low renin values, ARR screening is applied only if aldosterone is > 240 pmol/L (90pg/mL); DR values <5mIU/L are set to a minimum of 5 mUI/L and PRA values < 0.2 ng/mL/h to 0.2 ng/mL/h.

- 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.
- For patients not meeting the previous conditions, confirmatory testing is necessary, which can include aldosterone suppression with saline (typically the primary test), fludrocortisone, captopril (used if sodium loading is unsafe due to severe heart issues), as well as renin stimulation with furosemide.

The figure below resumes the first diagnosis steps and confirmatory testing in patients with suspected PA.

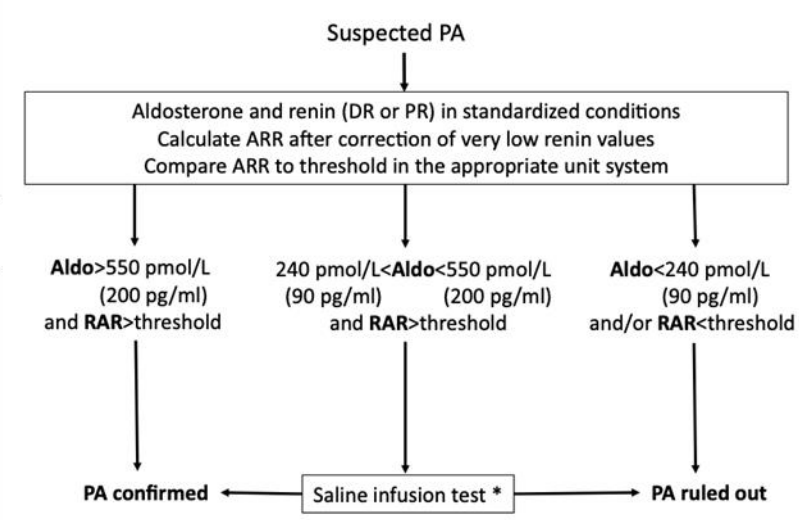

Figure 2. *Diagnosis Steps and Confirmatory Testing in Patients with Suspected PA*

24-hour urinary ionogram

Urinary ionograms offer two valuable functions: first, they help confirm that renal leakage is the cause of hypokalemia, and second, they assist in assessing sodium levels. For effective screening, it's advisable to include measurements of urinary potassium and sodium levels to assess sodium load. As a result, we recommend incorporating a comprehensive screening approach that includes not only a blood ionogram and ARR estimate but also a 24-hour urinary ionogram, measuring urinary sodium, potassium, and creatinine levels.

Urinary aldosterone

The urinary aldosterone assay is frequently employed for screening or diagnosing aldosterone-related conditions and appears to offer advantages over relying solely on plasma aldosterone levels. However, its sensitivity is lower compared to the ARR. Consequently, it is not typically used as a primary screening criterion for PA.

N-terminal probrain natriuretic peptide

In the future, N-terminal probrain natriuretic peptide might complement the use of ARR as a potential marker for PA. It shows a positive correlation with ARR, a negative correlation with renin levels, and could independently identify patients who are likely to respond positively to the IV saline suppression test, indicating a higher risk of confirmed PA.

1.2.1.3 Subtype Diagnosis of PA

Etiological diagnosis concerns only those patients in whom PA has been confirmed and mainly aims to distinguish PA with and without lateralized secretion.

Except for rare cases involving type 1 or 3 FH, which can be diagnosed genetically, the diagnosis of lateralized aldosterone secretion is typically made through adrenal Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) and adrenal venous sampling (AVS) (level of evidence +).

CT or MRI are recommended in all cases of PA. These imaging studies may exceptionally reveal adrenocortical carcinoma, in which case the surgical approach aims to address the cancer. Otherwise, the imaging typically shows either normal or hyperplastic adrenal glands or a unilateral adenoma.

However, it's important to note that relying solely on imaging carries a risk of false positives in patients over 35 years of age (indicating non-aldosterone-secreting adenomas) and false negatives in all patients (indicating unilateral hyperplasia).

It is suggested that individuals aged 35 and older who are potential candidates for surgery should undergo AVS. It compares aldosterone/cortisol ratio between the two adrenal veins to screen for lateralized secretion. This procedure should be conducted simultaneously in both adrenal veins, without the need for ACTH stimulation. To validate the sampling results, it's important to perform an adrenal vein cortisol assay, which should reveal a concentration at least twice as high as that found in the peripheral veins. A recent international consensus statement proposed a selectivity index threshold of ≥ 2 to validate AVS and an LI threshold of ≥ 2 to confirm lateralization of hypersecretion (level of evidence ++).

Two radiopharmaceuticals have been described: ^{131}I- methylnorcholesterol, which accumulates in the adrenocortical gland under the influence of ACTH, and ^{11}C-metomidate, an 11ß hydroxylase and aldosterone-synthase inhibitor. They are not yet widely recommended (level of evidence +).

Postural stimulation tests with 40mg furosemide are not recommended.

The figure below resumes the subtype diagnosis of PA.

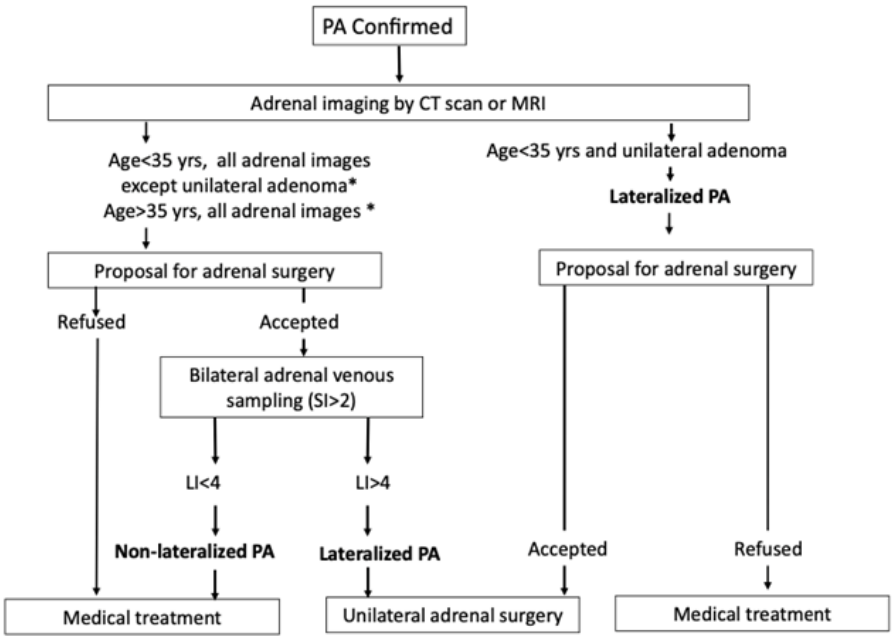

Figure 3. *Subtype Diagnosis of PA*

1.2.1.4 Treatment of PA

The choice of treatment approaches for PA depends on its specific type. When PA is lateralized or caused by a Conn's adenoma, a laparoscopic unilateral adrenalectomy may be recommended. In cases of non-lateralized PA, it is generally agreed that adrenalectomy is not the preferred option, and medical treatment is widely favored; it also serves as an alternative in lateralized forms of PA.

Lateralized PA[9]

The primary goal of treating PA is to prevent or correct hypertension, hypokalemia, and damage to target organs.

Except for adrenocortical carcinoma, which is rare, the adrenal lesions responsible for lateralized PA are typically small and benign. This characteristic makes them well-suited for laparoscopic surgery (trans or retroperitoneal approach) that should be done by an experienced surgeon in a reference center.

Laparoscopic adrenalectomy carries a lower risk of perioperative complications, including those related to the abdominal wall, infection, respiration, or cardiovascular issues, compared to open surgery. Additionally, it enables a shorter hospital stay (strong, evidence +++).

There is no proven advantage of partial adrenalectomy or non-surgical ablation over total adrenalectomy (weak, evidence +), which effectively corrects hypokalemia,

improves blood pressure control, and reduces the need for medication in 40% of cases.

The management of specific complications may be necessary during laparoscopic surgery:

- The systolic BP typically increases by an average of 20–30 mmHg above the usual levels, requiring antihypertensive medications in approximately 45% of cases (strong, evidence +).
- The serum potassium levels decrease by an average of 0.5–1 mmol/l during adrenalectomy when compared to preoperative levels Therefore, it is essential to normalize potassium levels just before the surgery (strong, evidence +).
- Postoperative hyperaldosteronism may occur. Administering spironolactone in the weeks leading up to the surgery may help by counteracting the inhibitory effects of aldosterone on the normal adrenal gland (strong, evidence +).

Additionally, the management of specific complications may also be necessary after laparoscopic surgery:

- Postoperative hyperkalemia due to functional mineralocorticoid insufficiency in the contralateral adrenal was reported. Spironolactone and potassium supplementation should be interrupted (strong, evidence +).
- BP and kalemia should be monitored postoperatively. Antihypertensive treatment should be resumed in case of post- operative hypertension.
- Fludrocortisone should be administered in case of persistent symptomatic hyperkalemia or hypotension (Strong, evidence +)

In persistent postoperative hypertension or hypokalemia, hormonal analysis may diagnose persistent PA and guide further treatment.

The advantage of opting for adrenalectomy over medical treatment lies in the lower long-term economic cost and reduced psychological burden of medication. Younger patients, given their longer life expectancy and lower anesthesia-related risk, make ideal candidates for surgical intervention. Additionally, individuals who struggle with spironolactone tolerance or face issues with medication adherence are also well-suited for surgery. In contrast, older patients tend to have a shorter life expectancy, a higher surgical risk and are more inclined to lean towards medical management.

Keeping in mind that medical and surgical treatment can be said to show comparable efficacy in terms of hypertension, hypokalemia and the cardiac and renal impact of PA, the decision regarding treatment heavily relies on the patient's preferences and should be made collaboratively after providing clear and impartial information.

Non lateralized PA[10]

In cases where PA is not localized, adrenalectomy is consensually not indicated, although one study did suggest some potential benefit. Therefore, medical treatment is generally recommended in these cases, focusing on preventing hypertension, hypokalemia, and any damage to target organs. The table below summarizes the recommended medical treatment.

Table 2. Summary of the Medical Treatment for the Non-Lateralized PA

Mechanism Of Action	Indication	Dose	Side effects	Level of evidence
SPIRONOLACTONE*				
Antagonist of both aldosterone and androgen receptors Agonist of the progesterone receptor. Mineralocorticoid receptor antagonist.	First line therapy in non-localized PA. Alternative therapy in localized PA.	50 to 400 mg daily	Gynecomastia, menstrual disorders, reduces testicular testosterone production, mastodynia.	Strong, Evidence +++
AMILORIDE*				
Potassium sparing diuretic	In case of spironolactone intolerance, amiloride may be used as replacement or in association with low-dose spironolactone. In case of non-controlled hypokalemia with spironolactone intolerance, amiloride should be preferred.	10 to 40mg daily for 6 months	Hyperkalemia	Strong, Evidence +++
EPLERENONE*				

Weaker but more selective inhibitory action than spironolactone.	Eplerenone may be used in case of spironolactone intolerance when amiloride proves ineffective.	50 to 300mg daily, in divided doses	Less side effects than spironolactone	Strong, Evidence +

*Spironolactone normalizes blood pressure, kalemia and aldosterone/renin ratio. Its use is beneficial in cases of PA associated hypertension and hypokalemia. It can also reduce the impact on target organs like the heart and the kidneys.

**Complementary medication was needed in most cases to normalize blood pressure

***Diastolic blood pressure fell less under eplerenone than spironolactone (−5.6 vs. −12.5 mm Hg), but there were more frequent side-effects under spironolactone.

Other medications

- Dihydropyridinic calcium channel blockers act as MRAs, and moreover blocks MR co-activators and suppress the expression of genes induced by aldosterone.
- Aldosterone synthase inhibitors: aldosterone is produced by conversion of cholesterol. The final stages of conversion involve cytochrome P450 aldosterone synthase and 11ß - hydroxylase enzymes encoded by the CYP11B2 and CYP11B1 genes, respectively. Selective aldosterone synthase inhibitors efficiently reduce aldosterone levels.
- Cyanodihydropyridines, a recent development, show excellent mineralocorticoid receptor antagonism while not affecting calcium channels. They are currently undergoing animal trials, and there have been no reported human phase I studies as of now.

1.3 North American Guidelines

1.3.1 Canadian Cardiovascular Society Guidelines for the Prevention, Diagnosis, Risk Assessment, and treatment of Hypertension in Adults and Children (2020)

Hypertension Canada's 2020 guidelines offered extensive, evidence-based recommendations for the prevention, diagnosis, risk assessment, and treatment of hypertension. Notably, the guidelines introduce fresh insights into managing resistant hypertension due to PA. The recommendations are summarized below[11]:

1.3.1.1 Screening

- Screening for PA is advisable in hypertensive patients who meet the following criteria (Grade D):
    - Unexplained spontaneous hypokalemia (potassium level < 3.5 mmol/L) or severe hypokalemia induced by diuretics (potassium level < 3.0 mmol/L).
    - Resistance to treatment with three different medications.
    - Discovery of an incidental adrenal adenoma.
- The preferred screening test for PA is the ARR.
    - Obtain samples in the morning after the patient has been mobile (sitting, standing, or walking) for a minimum of 2 hours.
    - Patients should be seated for 5-15 minutes before the blood draw.
    - Ensure that any hypokalemia is corrected and encourage liberal sodium intake.
    - To minimize interference, discontinue agents significantly affecting test results (e.g., aldosterone antagonists, potassium-sparing and -wasting diuretics) at least 4-6 weeks before testing.
    - If results are inconclusive, and hypertension can be managed with medications less likely to impact testing (e.g., slow-release verapamil, diltiazem, hydralazine, prazosin, doxazosin, and terazosin), repeat testing after withdrawing the following medications that may affect accuracy: beta-blockers, centrally acting alpha-2 agonists, angiotensin receptor blockers, ACE inhibitors, direct renin inhibitors, and dihydropyridine calcium channel blockers.
    - Note that false-positive results might occur with direct renin mass/concentration in women using oral contraceptive pills. If possible, discontinue oral contraception for one month before testing, or alternatively, measure plasma renin activity instead.

1.3.1.2 Confirmatory testing

- Saline Loading Tests (choose one):
    - Administer 2 liters of normal saline intravenously over 4 hours in a reclined position. Note that this test is not recommended for individuals with severe, uncontrolled hypertension or congestive heart failure. PA is confirmed if post-infusion plasma aldosterone exceeds 280 pmol/L. If

it's less than 140 pmol/L, PA is unlikely. Values in between are considered inconclusive.

- Administer more than 200 mmol/d of oral sodium (equivalent to over 5 g/d of sodium, over 12 g/d of sodium chloride, or over 2 tsp/d of salt) for 3 days. PA is confirmed if 24-hour urinary aldosterone exceeds 33 nmol/d (measured from the morning of day 3 to the morning of day 4). If it's less than 28 nmol/d, primary aldosteronism is unlikely.

- A plasma aldosterone to plasma renin activity ratio exceeding 1400 pmol/L/ng/mL/h (or > 270 pmol/L/ng/L), along with a plasma aldosterone level surpassing 440 pmol/L.
- Captopril Suppression Test:
  - Administer 25-50 mg of captopril orally after the patient has been seated or standing for 1 hour.
  - While seated, measure renin and plasma aldosterone levels at time 0 and 1 to 2 hours after captopril ingestion.
  - If plasma aldosterone is suppressed by over 30% after captopril ingestion, PA is unlikely. In cases of PA, plasma aldosterone remains elevated while renin levels remain suppressed.

1.3.1.3 Subtype classification

- **Localization of Adrenal Lesion**:
  - CT scanning or MRI can help identify adrenal lesions.
  - An adrenal lesion or adenoma may appear on imaging, but it might not necessarily be functional.
  - If surgery is being considered to remove a suspected unilateral source of PA, it is advisable to perform selective AVS first. This verifies if the abnormally appearing adrenal gland is indeed the source of aldosterone overproduction and distinguishes between unilateral and bilateral overproduction of aldosterone.
- **Genetic Testing for GRA**:

Consider selective genetic testing for GRA in patients with confirmed PA and either of the following:

- A family history of primary aldosteronism or stroke occurring at a young age (≤ 40 years)
- Onset of hypertension at 20 years of age or younger, along with negative imaging results.

1.3.1.4 Treatment

- **Surgery for Unilateral Hypersecretion**: In patients with confirmed PA and a definite adrenal mass who are candidates for surgery, it is recommended to perform AVS to determine the side of aldosterone overproduction. This procedure should be carried out exclusively by experienced teams working at specialized centers (Grade C).
    - Consider ipsilateral adrenalectomy for unilateral forms of hypersecretion, such as APAs.
    - After surgery, closely monitor patients because a significant number may still have hypertension.
- **MRAs for Bilateral Disease**
    - MRAs, especially low to moderate doses of spironolactone, are effective for individuals with bilateral disease, such as IHA or bilateral adrenal hyperplasia.
    - Regular monitoring of potassium and creatinine levels is essential, especially when used in combination with angiotensin receptor blockers or ACE inhibitors.
- **MRAs for Non-Surgical Candidates**
    - Consider MRAs for individuals who are not suitable candidates for surgery or who refuse surgery, even if unilateral hypersecretion is confirmed.
    - Responses to other antihypertensive medications like angiotensin receptor blockers, ACE inhibitors, and calcium channel blockers are often only moderately effective.
- **Renal Monitoring after Treatment**
    - PA can lead to relative hyperfiltration injury to the kidneys beyond what is observed in essential hypertension.
    - Treatment of PA, either through surgery or medical therapy, may reveal significant underlying renal issues, resulting in increased creatinine levels and reduced estimated glomerular filtration rate.
    - Patients should undergo close monitoring of their renal function after treatment.

1.4 International Guidelines

1.4.1 Endocrine Society Clinical Practice Guideline of the Management of Primary Aldosteronism (2016)

The Task Force was comprised of a chair appointed by the Clinical Guidelines Subcommittee of the Endocrine Society, six additional experts, a methodologist, and a medical writer. The guideline was jointly sponsored by the American Heart Association, American Association of Endocrine Surgeons, European Society of Endocrinology, European Society of Hypertension, International Association of Endocrine Surgeons, International Society of Endocrinology, International Society of Hypertension, Japan Endocrine Society, and The Japanese Society of Hypertension. A search for systematic reviews and primary studies to formulate the key treatment and prevention recommendations was conducted. The Task Force is confident that patients who follow the strong recommendations will generally experience more benefit than harm. In the case of weak recommendations, it is essential to carefully assess the patient's individual circumstances, values, and preferences to determine the most suitable course of action. The recommendations are summarized below[12].

1.4.1.1 Case detection

- PA should be actively screened for in specific patient groups. These groups include individuals with persistent high BP readings exceeding 150/100 mm Hg in three separate measurements taken on different days. PA screening is also recommended for those with hypertension (BP >140/90 mm Hg) that doesn't respond to three different standard antihypertensive medications, including a diuretic, or individuals whose blood pressure remains controlled (<140/90 mm Hg) but require four or more antihypertensive drugs. Additionally, screening is advised for patients with hypertension and either spontaneous or diuretic-induced hypokalemia, adrenal incidentalomas, sleep apnea, a family history of early-onset hypertension, or a history of cerebrovascular accidents at a young age (<40 years). Moreover, all first-degree relatives of individuals already diagnosed with PA who have hypertension should also be screened for the condition. These screening criteria aim to identify potential cases of PA for further assessment and management. (1I⊕⊕○○)
- We recommend using the plasma ARR to detect possible cases of PA in these patient groups. (1I⊕⊕⊕○)
    - The ARR test is most sensitive when blood samples are collected in the morning, typically after patients have been out of bed for at least 2 hours and seated for 5–15 minutes.

- Ideally, patients should maintain their usual dietary salt intake before the test and should have adequate potassium levels.
- MRAs should be discontinued for at least 4 weeks before ARR testing.
- Currently, the ARR is the most reliable screening method for PA. Although comprehensive test characteristic estimates for the ARR are limited due to study design limitations, multiple studies have shown its superiority in measuring potassium and aldosterone (both of which have lower sensitivity) or renin (which is less specific) individually. Importantly, laboratories should report individual values for both plasma aldosterone concentration and plasma renin activity or plasma renin concentration, as well as the calculated ARR.
- The ARR, like other biochemical case detection tests, is subject to false positives and false negatives (medications and certain conditions can impact the ARR). In cases where the initial results are inconclusive or challenging to interpret due to suboptimal sampling conditions, or when there is strong clinical suspicion of PA despite negative initial screening results, it is advisable to repeat the test.

1.4.1.2 Case confirmation

- Rather than immediately proceeding to subtype classification, we recommend that patients with a positive ARR undergo one or more confirmatory tests to conclusively establish or rule out the diagnosis. (1I⊕⊕○○) Nevertheless, when spontaneous hypokalemia occurs and plasma renin levels are undetectable, but plasma aldosterone concentration exceeds 20 ng/dL (550 pmol/L), we suggest that further confirmatory testing may not be necessary. (2I⊕○○○)
  - The existing literature does not establish a definitive "gold standard" for confirming PA. Most studies have retrospectively assessed test performance in relatively small patient cohorts chosen based on a high pretest probability of PA. Additionally, these studies often compare various tests rather than aiming for a conclusive diagnosis of PA.
  - Four different testing procedures, including oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge, are commonly employed, with fludrocortisone suppression also being used in Japan.
  - There is no conclusive evidence that any single test is superior, and there is insufficient direct evidence to endorse one above the rest. While these tests may vary in terms of their sensitivity, specificity, and reliability, the

selection of a confirmatory test is typically influenced by factors such as cost, patient adherence, laboratory protocols, and local expertise.

- Exercise caution when performing confirmatory tests that involve oral or intravenous sodium loading in patients with uncontrolled hypertension or congestive heart failure.
- Avoid the use of furosemide in individuals at risk of arrhythmias.

1.4.1.3 Subtype classification

- ❖ We recommend that all patients with PA undergo adrenal CT during the initial evaluation for subtype testing. This is done to rule out the presence of significant masses that could potentially indicate adrenocortical carcinoma and to provide assistance to the interventional radiologist and surgeon when anatomically relevant. It's important to note that MRI does not offer any advantages over CT in the evaluation of PA subtypes, as it is both more expensive and has lower spatial resolution compared to CT. (1|⊕⊕⊕○)
  - Clinicians use findings from adrenal CT scans, including normal appearance, unilateral macroadenomas (>1 cm), minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macro- or microadenomas (or a combination) in combination with AVS and ancillary tests to make treatment decisions in patients with PA.
  - APAs typically appear as small hypodense nodules, often less than 2 cm in diameter, on CT scans. Idiopathic Adrenal Hyperplasia can result in normal CT appearances or nodular changes in the adrenal glands.
  - Adrenal CT has limitations: Small APAs can be misinterpreted as "IHA" when CT shows bilateral nodularity or normal-appearing adrenals. Apparent adrenal microadenomas may actually represent hyperplasia or nonfunctioning nodules, making unilateral adrenalectomy inappropriate.
  - AVS is essential for guiding appropriate therapy in PA patients seeking a potential surgical cure.
  - CT is valuable for detecting larger lesions (>4 cm) that may require removal due to malignant potential. It helps localize the right adrenal vein for cannulation during AVS. CT findings can be particularly helpful in young patients with severe PA.
- ❖ We recommend that, when surgical treatment is both possible and preferred by the patient, an experienced radiologist should conduct AVS to differentiate between unilateral and bilateral adrenal conditions. (1|⊕⊕⊕○) In the case of younger patients (under 35 years old) experiencing spontaneous hypokalemia, substantial aldosterone overproduction, and unilateral adrenal lesions

exhibiting radiological characteristics consistent with cortical adenomas on adrenal CT scans, AVS may not be necessary prior to undergoing unilateral adrenalectomy. (2|⊕○○○)

- Differentiating the source of excessive aldosterone secretion, whether unilateral or bilateral, is crucial in managing PA. Unilateral adrenalectomy typically normalizes hypokalemia and improves hypertension in all patients with APAs or Unilateral Adrenal Hyperplasia (UAH). In cases of bilateral IHA and GRA, adrenalectomy rarely corrects hypertension, making medical therapy the preferred treatment. Medical management may also be considered for unilateral disease when surgery is not feasible or if the patient declines.
- AVS is costly and invasive, and it's essential to avoid this test in patients without PA. It has superior sensitivity (95%) and specificity (100%) for detecting unilateral aldosterone excess compared to adrenal CT (sensitivity 78%, specificity 75%). AVS is considered the "gold standard" for distinguishing unilateral (APAs or UAH) from bilateral (IHA) disease in PA patients. While it can be challenging, especially in cannulating the right adrenal vein, the success rate typically improves with experience, ranging from 90% to 96%.

❖ For patients who develop confirmed PA before the age of 20 or have a family history of PA or an early-onset stroke (under 40 years of age), it is advisable to consider genetic testing for FH-I related to the GRA gene. In cases of very young patients diagnosed with PA, it is recommended to explore testing for germline mutations in KCNJ5 associated with FH-III. (2|⊕○○○)

- Genetic testing using Southern blot or long PCR techniques is highly sensitive and specific for GRA and should replace indirect testing methods, such as measuring urinary levels of 18-oxocortisol and 18-hydroxy-cortisol or performing dexamethasone suppression tests, which can be misleading.

1.4.1.4 Management of PA

❖ We recommend for patients with confirmed unilateral PA, specifically those diagnosed with APAs or UAH, unilateral laparoscopic adrenalectomy. However, in cases where a patient is either unable or unwilling to undergo surgical intervention, our recommendation shifts towards medical management, which includes the use of MRAs. Likewise, for patients testing positive for ARR but facing constraints or reluctance in pursuing further diagnostic investigations, our recommendation remains consistent with medical treatment involving MRAs. (1|⊕⊕○○)

- Approximately 50% of patients with APAs experience a "cure" of hypertension, defined as BP <140/90 mm Hg without antihypertensive medication. Adrenalectomy leads to a significant and sustained reduction in left ventricular mass index and volume, improving diastolic dysfunction. It also reverses carotid intima-media thickness and arterial stiffness.
- Laparoscopic adrenalectomy is preferable to open adrenalectomy due to shorter hospital stays and fewer complications.
- Patients who do not undergo surgery are managed with medical therapy, typically spironolactone or amiloride, which reduces BP but often requires additional antihypertensive medications due to side effects.
- Long-term, adrenalectomy proves more cost-effective than lifelong medical therapy for unilateral PA patients, considering the elimination of medication or reduction in side effects. Hence, unilateral laparoscopic adrenalectomy is the preferred treatment for unilateral PA.
- Prior to surgery, it is crucial to effectively control both hypertension and hypokalemia in patients.
- After surgery, healthcare providers should promptly measure plasma aldosterone and renin activity levels to assess the early biochemical response, although renin levels may not immediately decrease. Potassium supplementation should be discontinued on the first day after surgery, and spironolactone should be stopped. Additionally, antihypertensive therapy should be reduced if deemed appropriate. Intravenous fluids administered postoperatively should primarily consist of normal saline without potassium chloride, unless serum potassium levels remain critically low (i.e., <3.0 mmol/L).
- In the initial weeks following surgery, patients should be advised to maintain a sodium-rich diet to prevent hyperkalemia. Predictors of postoperative hyperkalemia include reduced preoperative glomerular filtration rate, elevated serum creatinine levels before surgery, increased creatinine levels post-surgery, and the development of microalbuminuria.
- In some cases, up to 5% of adrenalectomized patients may experience persistent hypoaldosteronism necessitating mineralocorticoid replacement therapy, such as fludrocortisone.
- BP typically normalizes or shows maximum improvement within 1 to 6 months after unilateral adrenalectomy for unilateral APAs. However, in

some patients, blood pressure improvement may continue for up to 1 year.

- For individuals with PA resulting from bilateral adrenal disease, our recommendation is to pursue medical treatment involving MRAs. (1|⨁⨁○○) We suggest spironolactone as the primary choice, with eplerenone as a secondary option (2|⨁○○○)
    - A randomized controlled trial showed that spironolactone might be more effective than eplerenone in controlling BP in patients with PA. Conversely, a smaller study found that eplerenone and spironolactone were equally effective in reducing BP in confirmed PA patients.
    - A low dose of a thiazide diuretic, triamterene, or amiloride can be added to potentially reduce the need for a higher dose of spironolactone, which may lead to side effects.
    - Eplerenone is a more recent, selective MRA that lacks antiandrogen and progesterone agonist effects, thereby reducing the occurrence of adverse endocrine side effects. It has approximately 50% of the MRA potency of spironolactone. Its improved tolerability profile should be weighed against its higher cost and the possibility that spironolactone may offer more effective blood pressure reduction in the medical treatment of PA. Due to its shorter half-life, eplerenone is typically administered twice daily for optimal effectiveness.
    - Other agents: Among the available epithelial sodium channel antagonists, amiloride and triamterene, amiloride has been studied more extensively as a potential treatment for PA. Although less effective than spironolactone, amiloride has its advantages. As a potassium-sparing diuretic, it can address both hypertension and hypokalemia in PA patients and is generally well-tolerated. Importantly, it does not produce the sex steroid-related side effects associated with spironolactone. However, amiloride does not provide the same beneficial effects on endothelial function. Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers have been examined in only a limited number of PA patients. Generally, they are antihypertensive without significantly affecting MR activation. Nevertheless, they are commonly used in combination with MRAs to lower blood pressure when it remains elevated.
- For individuals with GRA, our primary treatment recommendation is to initiate therapy with the minimum effective dose of glucocorticoid, aiming to reduce ACTH levels and subsequently normalize BP and potassium levels. In addition, if BP fails to normalize with glucocorticoid alone, a MRA may be added. GRA

should primarily be managed through medical treatment involving a glucocorticoid to partially suppress pituitary ACTH secretion. (1I⨁○○○)

- We recommend the use of a synthetic, longer-acting glucocorticoid, such as dexamethasone or prednisone, to effectively suppress ACTH secretion. Ideally, this glucocorticoid should be administered at bedtime to counteract the early morning ACTH surge.
- It is crucial to prevent overtreatment with exogenous steroids to avoid iatrogenic Cushing's syndrome and impaired linear growth in children, which can result from excessive dosing.

1.4.2 Japan Endocrine Society Clinical Practice Guideline for the Diagnosis and Management of Primary Aldosteronism (2021)

The Japan Endocrine Society has formulated a novel clinical practice guideline and has provided appropriate recommendations for the diagnosis and treatment of PA, drawing upon the available evidence predominantly from Japan and aligning with Japan's medical insurance system[13]. The recommendations are summarized below:

Unilateral Disease

- Adrenalectomy is recommended for patients with unilateral PA (1A):
  - The success rate of curing hypertension through adrenalectomy in unilateral PA patients is influenced by several factors, including: The number of antihypertensive medications taken before surgery, the duration of hypertension, gender, age, and renal function (B).
  - An early decrease in estimated Glomerular Filtration Rate (eGFR) following adrenalectomy is indicative of a favorable long-term renal function outcome. High plasma aldosterone concentration and hypokalemia are significant predictors of the initial eGFR decline after adrenalectomy (C).
- Preoperative Complication Management:
  - It is recommended to address complications before adrenalectomy to reduce anesthesia and surgery risks (1B).
  - MRAs are recommended as the initial medication to manage hypertension and hypokalemia before adrenalectomy (1B).
- Postoperative Monitoring and Management:
  - We recommend vigilant monitoring and control of serum potassium levels and renal function (1B).

- Risk factors for post-adrenalectomy hyperkalemia: Elderly age, low eGFR, and suppressed aldosterone secretion on the non-dominant adrenal side (C).
- Glucocorticoid replacement therapy post-adrenalectomy for patients with unilateral PA co-secreting cortisol is recommended (1B).

Bilateral Disease

❖ Medical treatment with MRAs is recommended for patients with bilateral PA or unilateral PA without surgery indication or patient preference (First-line Therapy) (1A):

- Treatment goals with MRAs include normalization of blood pressure, restoration of serum potassium concentrations and relief of renin suppression (1B)
- Three MRAs are approved in Japan: Spironolactone, Eplerenone and Esaxerenone. Start with a low MRAs dose and carefully monitor serum potassium levels and renal function.
- If hypertension isn't controlled with MRAs alone, consider adding other antihypertensive medications. Calcium channel blockers are a suitable option (minimal effect on fluid volume and renal function).
- If severe refractory hypokalemia, consider combining MRAs with potassium preparations. Eplerenone or esaxerenone are contraindicated with potassium preparations.
- The choice of MRAs should consider several factors: Antihypertensive effectiveness, the impact on improving target organ damage due to hypertension, adverse effects, tolerability, gender considerations, medical costs, in addition to usage precautions (1A).
- There is a lack of evidence indicating differences among MRAs in their effects on long-term prognosis and target organ damage in PA patients. Selection of the appropriate MRA may be influenced by approved doses and usage precautions (B).
- Gynecomastia (in males) and breast pain (in females) are more common side effects associated with spironolactone compared to other MRAs due to its lower selectivity to the mineralocorticoid receptor.

Special Considerations

❖ For pregnant patients with PA, the treatment approach involves controlling hypertension using approved antihypertensive medications for pregnancy

and normalizing hypokalemia with potassium preparation. The recommended antihypertensive medications approved for pregnancy are: α-methyldopa, hydralazine, labetalol, and nifedipine after the 20th week of pregnancy (1B).

- We recommend MRAs for the treatment of PA, even in patients with well-controlled BP and normal potassium levels through standard medication. This is to prevent target organ damage through the direct action of aldosterone (1C).
- Adrenalectomy surpasses MRAs in terms of its antihypertensive effects. Adrenalectomy is equally or more effective than MRAs in addressing hypokalemia, halting the advancement of target organ damage, and enhancing overall life prognosis (B).

Section 2.0 Drug Therapy

2.1 Mineralocorticoid Receptor Antagonists (MRAs)

2.1.1 Spironolactone

Information on Spironolactone is detailed in the table below[14].

Table 3. Spironolactone Drug Information

SCIENTIFIC NAME SPIRONOLACTONE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E26
Drug Class	POTASSIUM SPARING AGENTS
Drug Sub-class	ALDOSTERONE ANTAGONIST
ATC Code	C03DA01
Pharmacological Class (ASHP)	Aldosterone receptor antagonist
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Initial dose: 12.5 to 25mg once daily. Gradually titrate to the lowest effective dose.
Maximum Daily Dose Adults*	400 mg daily
Dose (pediatrics)	1 to 3mg/kg/day
Maximum Daily Dose Pediatrics*	100mg daily
Adjustment	Renal impairment: • eGFR >50 mL/minute/1.73 m2: No initial dosage adjustment necessary. • eGFR 30 to 50 mL/minute/1.73 m2: Initial: 12.5 mg once daily or every other day; may double the dose every 4 weeks if serum potassium

	remains <5 mEq/L and kidney function is stable, up to a maximum target dose of 25 mg/day • eGFR <30 mL/minute/1.73 m2: Use not recommended; heart failure clinical trials excluded patients with serum creatinine ≥2.5 mg/Dl
Prescribing edits*	ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Unilateral Disease: In cases where a patient is either unable or unwilling to undergo surgical intervention, Spironolactone is considered as a **secondary option**.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Hyperkaliemia, Gynecomastia.
Drug Interactions*	**Category X:** • Bromperidol • Cyclosporine • Potassium salts • Potassium sparing diuretics.
Special Population	Older adults, Surgical patients.
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Spironolactone and its active metabolite are present in breast milk. Breastfeeding is considered acceptable.
Contraindications	Hyperkalemia, Addison disease, concomitant use with eplerenone.
Monitoring Requirements	• Blood pressure

	• Heart rate • Serum electrolytes
Precautions	Fluid and electrolyte imbalance
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for spironolactone in PA. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Spironolactone

Spironolactone functions as an antagonist to the aldosterone receptor, giving it a mineralocorticoid effect. In patients with non-localized PA, adrenalectomy is not indicated, and spironolactone is considered a first-line treatment. The recommended starting dose is 12.5 to 25mg daily, with gradual titration until reaching the lowest effective dose. It is important to note that spironolactone may lead to fluid and electrolyte imbalances (e.g., hypomagnesemia, hyponatremia, hypocalcemia, hyperglycemia, hyperkalemia), so monitoring and addressing any potential imbalances is crucial during its use. Additionally, due to its androgen receptor antagonism, it may cause gynecomastia in men and menstrual disorders in women. There are no specific recommendations issued by the HTA bodies for spironolactone.

2.1.2 Eplerenone

Information on Eplerenone is detailed in the table below[15].

Table 4. Eplerenone Drug Information

SCIENTIFIC NAME EPLERENONE	
SFDA Classification	Prescription
SFDA	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	E26.0

Drug Class	POTASSIUM SPARING AGENTS
Drug Sub-class	ALDOSTERONE ANTAGONIST
ATC Code	C03DA04
Pharmacological Class (ASHP)	Aldosterone Receptor Antagonist
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Off-label use: Initial: 25 mg twice daily; gradually titrate to the lowest effective dose. For patients undergoing surgical intervention, administer the last dose of eplerenone on the day of surgery, then discontinue eplerenone on postoperative day 1.
Maximum Daily Dose Adults*	300 mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. Systemic exposure is increased in moderate hepatic impairment (Child-Pugh class B). **Kidney Impairment:** CrCl <50 mL/minute or serum creatinine >2 mg/dL (males) or >1.8 mg/dL (females): Use is contraindicated.
Prescribing edits*	ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Unilateral Disease: In cases where a patient is either unable or unwilling to undergo surgical intervention, Eplerenone is considered as a

	secondary option in spironolactone-intolerant patients.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**>10%:** -Endocrine and metabolic: Hyperkalemia (cardiac failure, post-myocardial infarction: 3%; >5.5 mEq/L: 16%; ≥6 mEq/L: 6%) **1% to 10%:** -Renal: Increased serum creatinine -Cardiovascular: Acute myocardial infarction, angina pectoris -Endocrine and metabolic: Gynecomastia, increased gamma-glutamyl transferase -Genitourinary: Abnormal vaginal hemorrhage -Nervous system: Dizziness, headache -Renal: Renal insufficiency
Drug Interactions*	**Category X:** -**Cyclosporine (Systemic):** Potassium-Sparing Diuretics may enhance the hyperkalemic effect of Cyclosporine. -**CYP3A4 Inhibitors (Strong):** May increase the serum concentration of Eplerenone. -**Fusidic Acid (Systemic):** May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). -**Potassium-Sparing Diuretics:** May enhance the hyperkalemic effect of other Potassium-Sparing Diuretics. -**Grapefruit juice** increases eplerenone AUC ~25%. Management: Dosage adjustments of eplerenone may be needed.
Special Population	**Beers Criteria:** Diuretics (eplerenone) are identified in the Beers Criteria as

	potentially inappropriate medications to be used with caution in patients 65 years and older due to the potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion or hyponatremia; monitor sodium concentration closely when initiating or adjusting the dose in older adults. **Pediatrics:** The safety and effectiveness of eplerenone have not been established in pediatric patients its use is not recommended in this patient population.
Pregnancy	Eplerenone could be the preferred choice when treating PA in patients who are planning pregnancy and need MRA. There is a lack of specific data regarding the treatment of PA during pregnancy. Patients diagnosed with PA should ideally discontinue eplerenone before becoming pregnant. However, if the condition is not well-managed without treatment, eplerenone may be resumed during the second or third trimester of pregnancy.
Lactation	Eplerenone is detectable in breast milk, as indicated by a case report. In this case, a dose of 50 mg of eplerenone was taken daily during pregnancy and continued after childbirth. Researchers collected several breast milk samples on postpartum days 7 and 35. The highest recorded eplerenone concentration in breast milk was 161.2 ng/mL, measured 4 hours after the dose on postpartum day 35. Using this milk concentration, the study authors calculated that the estimated daily dose of eplerenone delivered to the infant through breast

	milk was 0.024 mg/kg/day, which corresponds to 3% of the mother's dose adjusted for the infant's weight. The infant was partially breastfed (more than 50% of feedings), and no adverse effects were reported. Additionally, the infant's development appeared normal at 1 and 3 months.
Contraindications	-Serum potassium >5.5 mEq/L at initiation -CrCl ≤30 mL/minute -Concomitant use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir). -Hypersensitivity to eplerenone or any component of the formulation -Severe hepatic impairment (Child-Pugh class C) -Concomitant use with potassium supplements or potassium-sparing diuretics
Monitoring Requirements	• **BP** • **Serum potassium**: Prior to therapy, within the first week, 1 month after start of treatment or dose adjustment, then periodically as clinically indicated. • **Serum potassium and serum creatinine** within 3 to 7 days after initiating concurrent therapy with a moderate CYP3A inhibitor, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker, or nonsteroidal anti-inflammatory drug.
Precautions	· **Heart failure:** When evaluating a heart failure patient for eplerenone treatment, eGFR should be >30

	mL/minute/1.73 m^2 or creatinine should be ≤2.5 mg/dL (males) or ≤2 mg/dL (females) with no recent worsening and potassium should be <5 mEq/L with no history of severe hyperkalemia. Discontinue therapy if serum potassium cannot be maintained <5.5 mEq/L or if kidney function worsens. · **Hepatic impairment:** Use with caution in patients with moderate to severe hepatic impairment. · **Kidney impairment:** Use with caution in patients with mild kidney impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for Eplerenone in PA. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Eplerenone

Eplerenone functions as a selective antagonist to the aldosterone receptor. It lacks the unwanted hormonal effects seen with spironolactone, making it a preferred choice for patients concerned about such side effects. It is about half as potent as spironolactone in terms of MRA activity. However, it is essential to weigh its improved tolerability against its higher cost and the potential for spironolactone to offer more effective BP control in PA treatment. Eplerenone, prescribed at a dosage of 25 mg twice a day, is recommended primarily for individuals with PA caused by bilateral adrenal disease. It is also considered as a secondary option for those with unilateral disease who do not undergo surgery. Eplerenone's safety and efficacy have not been established in pediatric patients, and its use is not recommended in this age group. In older adults (65 years and older), caution is advised as it may potentially lead to or exacerbate hyponatremia. There are no specific recommendations issued by the HTA bodies for Eplerenone.

2.2 Corticosteroids

2.2.1 Prednisone

Information on Prednisone is detailed in the table below[16].

Table 5. Prednisone Drug Information

SCIENTIFIC NAME PREDNISONE	
SFDA Classification	Prescription
SFDA	No
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E26.0
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB04
Pharmacological Class (ASHP)	Glucocorticoids
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	2.5 to 7.5mg daily at bedtime
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Hydrocortisone is preferred
Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing edits*	
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A

EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effect (glaucoma).
Drug Interactions	**<u>Category X:</u>** • Aldesleukin • Brivudine • Brivudine • Cladribine • Desmopressin • Disulfiram • Mifamurtide • Natalizumab • Pimecrolimus • Ruxolitinib • Tacrolimus • Tertomotide • Vaccines like Mumps- Rubella- or Varicella-Containing Live Vaccines
Special Population	Pediatric, older patients.
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Prednisone and its metabolite, prednisolone, are present in breast milk. They are generally considered acceptable in breastfeeding women when used in usual doses; however, monitoring of the breastfeeding infant is recommended.
Contraindications	Hypersensitivity to prednisone, administration of live or live attenuated vaccines with immunosuppressive

	doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose • Growth in pediatric • Bone mineral density
Precautions	Hepatic and renal impairments, Myasthenia gravis, perforation risk in patients with GI diseases.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for prednisone in GRA. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Prednisone

Prednisone, a synthetic glucocorticoid derived from cortisone, is converted to prednisolone in the liver. It's an FDA-approved corticosteroid used to treat various diseases with anti-inflammatory or immunosuppressive effects. It is recognized for its efficacy in managing GRA, a hereditary cause of human hypertension in which aldosterone secretion is regulated by ACTH. The daily dose is 2.5 to 7.5mg daily. Adrenal suppression (tertiary adrenal insufficiency) may occur with prednisone, and results from inadequate stimulation of the adrenal glands. There are no recommendations issued by the HTA bodies for prednisone.

2.3 Other Drugs

2.3.1 Fludrocortisone[17]

- Prior to laparoscopic adrenalectomy, administering spironolactone normalizes BP, stabilizes electrolytes levels, and reduces the risk of postoperative hyperaldosteronism by counteracting aldosterone inhibition in the normal adrenal. However postoperative hyperkalemia due to functional mineralocorticoid insufficiency in the contralateral adrenal was reported in 15–30% of cases. This hyperkalemia is generally of moderate severity and transient. Interrupting both spironolactone and potassium supplementation during surgery is recommended, and postoperative kalemia levels should be

monitored, especially in cases of chronic kidney failure. Up to 5% of patients may require extended postoperative fludrocortisone treatment.

- Fludrocortisone is a potent mineralocorticoid with high glucocorticoid activity, used primarily for its mineralocorticoid effects. It promotes increased reabsorption of sodium and loss of potassium from renal distal tubules in case of persistent symptomatic hyperkalemia.
- The starting dose is 0.05 to 0.1 mg once daily in the morning, with a maintenance dose of 0.05 to 0.2 mg daily.
- Fludrocortisone is associated with cardiovascular effects, including hypertension (most commonly supine systolic) and heart failure with reduced ejection fraction. Additionally, it can lead to electrolyte imbalances, such as hypokalemia and hypomagnesemia, with an estimated incidence of 24% to 50% and approximately 5%, respectively.

2.3.2 Dexamethasone[18]

- For individuals with GRA, the primary treatment approach is to initiate therapy with the lowest effective dose of a glucocorticoid, to suppress pituitary ACTH secretion and subsequently normalizing BP and potassium levels. If blood pressure does not normalize with glucocorticoid alone, a MAR may be added.
- It is recommended to use a synthetic, longer-acting glucocorticoid, such as dexamethasone or prednisone, to effectively suppress ACTH secretion. Ideally, this glucocorticoid should be administered at bedtime to counteract the early morning ACTH surge. It is imperative to avoid excessive dosing of exogenous steroids to prevent overtreatment, which can lead to iatrogenic Cushing's syndrome and impaired linear growth in children.
- The usual dose is 0.125 mg to 0.25 mg daily at bedtime.
- Due to the potential for serious adverse reactions (growth suppression, interfere with endogenous corticosteroid production) in the breastfeeding infant, some manufacturers recommend discontinuing corticosteroids.

2.3.3 Amiloride and Triamterene[19,20]

- In case of spironolactone intolerance, amiloride has undergone more comprehensive studies as a potential treatment for PA than triamterene. While it may be less potent than spironolactone, amiloride offers distinct advantages. It functions as a potassium-sparing diuretic, effectively addressing both hypertension and hypokalemia in PA patients, and is

generally well-tolerated. Notably, it avoids the sex steroid-related side effects associated with spironolactone.

- For individuals with PA resulting from bilateral adrenal disease, the addition of a low dose of a thiazide diuretic, triamterene or amiloride may be considered to potentially reduce the requirement for a higher dose of spironolactone, thereby minimizing the risk of side effects.
- The usual dose of amiloride is 10 to 40mg daily for 6months.
- The usual dose of triamterene is 50 to 100 mg once daily; titrate as needed based on patient response. Maximum: 300 mg/day in divided doses
- Up to 10% of patients may experience hyperkalemia during amiloride and triamterene treatments. Careful monitoring of potassium serum levels is recommended.

Section 3.0 Key Recommendations

The primary goal in treating patients with PA is to reduce the associated risks of hypertension, hypokalemia, renal damage, and cardiovascular issues, ultimately leading to better overall health outcomes. This means that regardless of whether PA is caused by unilateral or bilateral adrenal disease, the treatment goals remain the same. These goals include counteracting the harmful cardiovascular effects of hyperaldosteronism, bringing serum potassium levels back to normal in patients with hypokalemia, and attaining normalized blood pressure.

All patients with PA should undergo adrenal CT as part of the initial evaluation for subtype testing. This helps rule out significant masses that may indicate adrenocortical carcinoma and aids interventional radiologists and surgeons in anatomical considerations. It's worth noting that MRI doesn't offer any advantages over CT for evaluating PA subtypes, as it's more expensive and has lower spatial resolution. Clinicians use findings from adrenal CT scans, in combination with AVS and ancillary tests, to guide treatment decisions in PA patients.

Accurate subtype diagnosis is crucial as the treatment approach for PA depends on its underlying cause:

Laparoscopic adrenalectomy

- For patients with confirmed unilateral disease (e.g., APAs, aldosterone-producing nodules, unilateral hyperplasia) by an experienced radiologist through AVS, a laparoscopic adrenalectomy (curative option) is recommended (1I⊕⊕⊕○). After surgery, close monitoring of BP and potassium levels should be performed.
- Postoperative hyperkalemia due to functional mineralocorticoid insufficiency in the contralateral adrenal can occur and recommends managing it with Fludrocortisone, a potent mineralocorticoid with high glucocorticoid activity (1I⊕○○○).
- In the long run, adrenalectomy proves greater cost-effectiveness compared to a lifelong course of medical therapy for unilateral PA patients, taking into account the discontinuation of medication or reduction in side effects. Therefore, unilateral laparoscopic adrenalectomy stands as the preferred treatment for unilateral PA.

Medical therapy

- If patients are either unable or unwilling to undergo surgical intervention, our recommendation shifts towards medical management, which includes the use of MRAs (1I⊕⊕○○).

- For ARR-positive patients with PA resulting from bilateral adrenal, MRAs are recommended: Spironolactone as a primary choice (1I⨁⨁⨁○). A randomized controlled trial showed that spironolactone might be more effective than eplerenone in controlling BP in patients with PA. A regular monitoring of potassium and creatinine levels is essential.
- For patients with IHA or specific genetic disorders (e.g., GRA, FH-III, IV): MRAs therapy is also suggested (2I⨁○○○)
- Amiloride or triamterene, which are potassium-sparing diuretics, are options to be considered when spironolactone and eplerenone are not well-tolerated (2I⨁○○○).
- In GRA cases: low-dose glucocorticoid (dexamethasone or prednisone) is recommended as an initial treatment to lower ACTH levels and normalize BP and potassium. If BP remains uncontrolled, consider adding MRAs (1I⨁○○○).

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of PA.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

We used the Grading of Recommendations, Assessment, Development, and Evaluation group criteria to describe both the quality of evidence and the strength of recommendations. We used “recommend” for strong recommendations and “suggest” for weak recommendations.

Both Task Forces used the best available research evidence to inform the recommendations, and both used consistent language and graphical descriptions of the strength of a recommendation and the quality of the evidence.

In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⨁◯◯◯ denotes very low quality evidence; ⨁⨁◯◯, low quality; ⨁⨁⨁◯, moderate quality; and ⨁⨁⨁⨁, high quality.

Grade A*	Recommendations for interventions are on the basis of randomized trials (or systematic reviews of trials) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes
Grade B*	Recommendations are on the basis of randomized trials, systematic reviews, or prespecified subgroup analyses of randomized trials that have lower precision, or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes
Grade C*	Recommendations are on the basis of trials that have lower levels of internal validity and/or precision, or trials for which unvalidated surrogate outcomes were reported, or results from nonrandomized observational studies
Grade D*	Recommendations are on the basis of expert opinion alone

* Grade is on the basis of the strength and quality of the clinical evidence. Factors such as patient preferences, cost, and/or resource intensiveness are not included in this grading schema.

Table 1 Certainty (strength) of the evidence level as a whole

Strength	Explanation
A (strong)	Confidence that the estimated effects support the recommendations is strong
B (medium)	Confidence that the estimated effects support the recommendations is moderate
C (weak)	Confidence that the estimated effects support the recommendations is limited
D (very weak)	Confidence that the estimated effects support the recommendations is uncertain

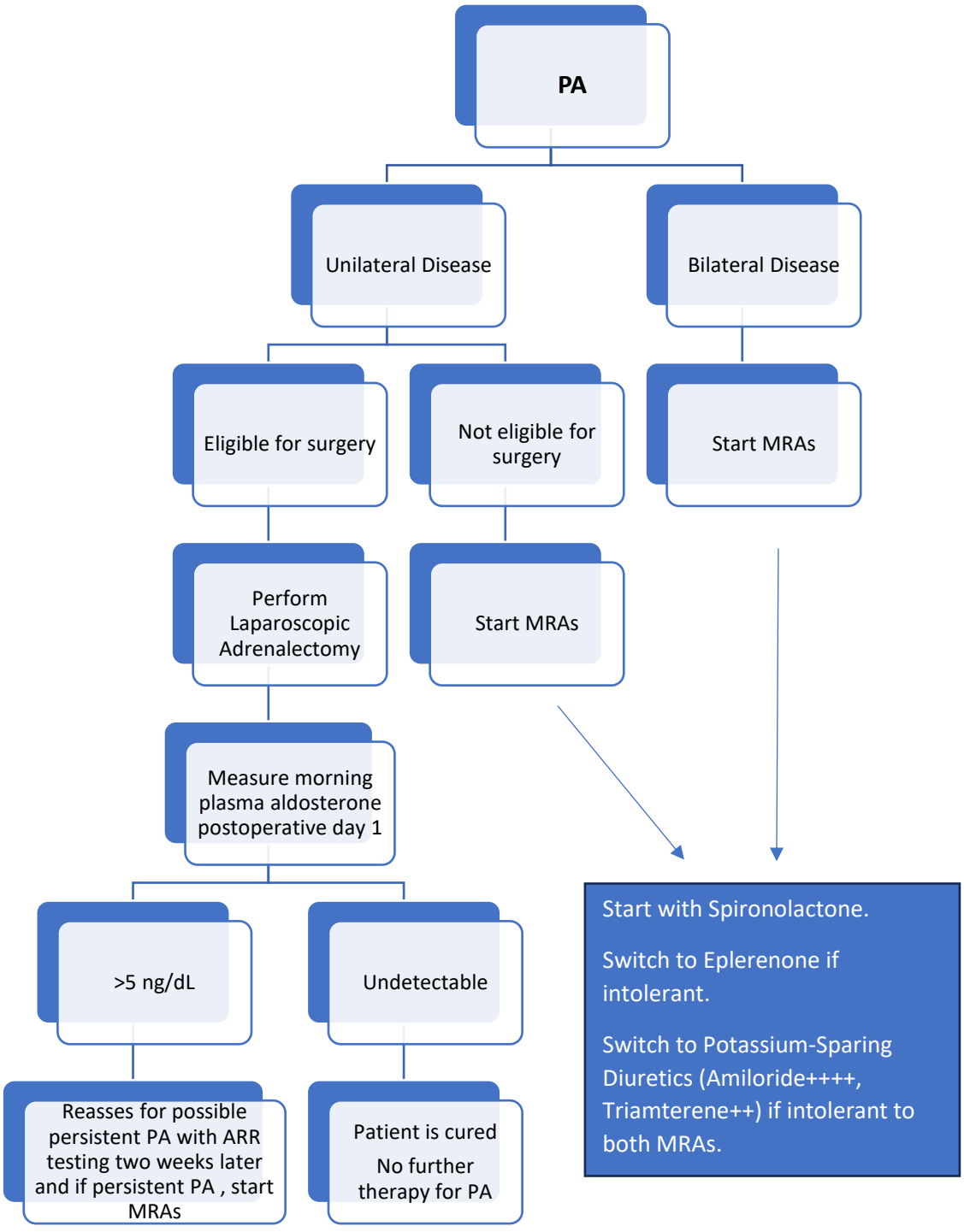
Table 2 Strength of the recommendations

Recommendation level	Explanation
1	It is recommended to "implement" or "not implement"
2	It is suggested to "implement" or "not implement"

Appendix C. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
(((((((primary hyperaldosteronism[MeSH Terms]) OR (Aldosteronism[Title/Abstract])) OR (Conn Syndrome[Title/Abstract])) OR (Syndrome, Conn[Title/Abstract])) OR (Primary Hyperaldosteronism[Title/Abstract])) OR (Hyperaldosteronism, Primary[Title/Abstract])) OR (Conn's Syndrome[Title/Abstract])) OR (Conns Syndrome[Title/Abstract])) OR (Syndrome, Conn's[Title/Abstract])	In the last 5 years	("Hyperaldosteronism"[MeSH Terms] OR "Aldosteronism"[Title/Abstract] OR "conn syndrome"[Title/Abstract] OR "syndrome conn"[Title/Abstract] OR "primary hyperaldosteronism"[Title/Abstract] OR "hyperaldosteronism primary"[Title/Abstract] OR "conn s syndrome"[Title/Abstract] OR "conns syndrome"[Title/Abstract] OR "syndrome conn s"[Title/Abstract]) AND (y_5[Filter])	1,949

Appendix D. Treatment Algorithm for PA



Abbreviations: PA: Primary Aldosteronism; ARR: Aldosterone-Renin Ratio; MRA: Mineralocorticoid-Receptor Antagonists.