
بسم الله الرحمن الرحيم

Primary

Hyperaldosteronism

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• Introduction

Primary hyperaldosteronism (PA) is one of the mos common forms of secondary hypertension. Althougthe prevalence of PA varies greatly depending on the study population, the prevalence of PA may be as high as 22% among individuals with resistant hypertension. Moreover, individuals with PA share a strikingly ,inordinate burden of cardiovascular disease compared with individuals with essential hypertension (EH).

Compared with individuals with EH, the presence of hyperaldosteronism increased the risk of myocardiai infarction, stroke, and atrial fibrillation (AF) on the magnitude of fourfold, sixfold, and 12-fold, respectively,Improved identification of individuals with PA is critical given the strong correlation between aldosterone and cardiovascular disease.

- **Etiology**

The **most prevalent cause** of primary hyperaldosteronism is aldosterone-producing **adenomas**.
Other causes include aldosterone-producing adrenal **carcinoma**, **ectopic** aldosterone secretion from the kidneys or ovaries, and **bilateral zona glomerulosa hyperplasia**. There are **familial** causes as well.
Type I is glucocorticoid-remediable hyperaldosteronism that results from the formation of a chimeric gene containing the regulator portion of **11B-hydroxylase** (usually regulated by ACTH) and the **synthetic region of aldosterone synthase**; as a result**, ACTH stimulates aldosterone synthase** and hence aldosterone production.
Type II causes are unclear; it correlates to a gene on 7p22 (band 11q13), and histologic findings are consistent with hyperplasia or adenomas.
Type III results from a mutation in **KCNJF** which is **a potassium channel** coding gene. This mutation causes increased **calcium ion availability into the glomerulosa cells** leading to increased aldosterone synthesis.

- **New Insights into Disease Prevalence**

  Some studies have shown that PA accounts for 5%-10% of patients with hypertension.

  A recently released, cross-sectional analysis has provided contemporary insights into the prevalence of PA.

  This study examined the prevalence of PA among 1000 patients from four geographically diverse centers in the United States. Two thirds of patients had adequate suppression of renin to assess renin-independen aldosterone production.

  The prevalence of primary aldosteronism among patients with normotension, stage 1 hypertension,stage 2 hypertension, and resistant hypertension was 11%, 16%, 22%, and 22%, respectively.

Besides demonstrating that PA is a more prevalent condition than previously thought (even among individuals who are normotensive and normokalemic), the authors described a spectrum of renin-independent aldosterone production that paralleled the severity of hypertension. Based on these results, it is apparent that our perception that PA is a rare disease needs to be reconsidered because, even among individuals with normotension, the prevalence of reninindependent hyperaldosteronism was high. Importantly, the clinical entity of PA may represent **a more clinically apparent and florid phase of a seemingly emerging spectrum of renin-independent, aldosterone-mediated hypertension.**

- **History and Physical**

A patient with suspected primary hyperaldosteronism will present with **uncontrolled hypertension** and will typically be **young**. These patients will require up to **three antihypertensive medications including a diuretic** to maintain suboptimal blood pressure control. They can also have a **family history of early-onset hypertension or cerebral vascular disease at a younger age**. Patients may have severe muscle weakness, palpitations, fatigue, or muscle cramps due to symptoms related to hypokalemia. Polydipsia and polyuria are present due to nephrogenic diabetes insipidus likely secondary to hypokalemia.

Hypokalemia has been considered one of the hallmark signs in the diagnosis of primary aldosteronism; however, estimates are **now that less than 37 percent** of patients who have primary hyperaldosteronism will present with hypokalemia. Patients who have **adequate sodium intake will often be more hypokalemic.** Increasing sodium intake will allow more sodium delivery to the cortical collecting tubules promoting further excretion of potassium in the setting of excess aldosterone. Even though patients typically do not present with hypokalemia; the diagnosis should be considered in a patient with **drug-resistant hypertension and hypokalemia in a patient starting a low dose of diuretic.**

There are no physical exam characteristics that will lead to a diagnosis of primary hyperaldosteronism. However, due to excessive hypertension and stress on the heart, left ventricular hypertrophy can occur leading to an S4 heart sound secondary to blood trying to enter a noncompliant stiff ventricle during atrial contraction. Other findings related to longstanding hypertension can arise throughout the body affecting the heart (heart failure), kidneys (proteinuria), eyes (hypertensive retinal changes), vasculature (carotid bruits/stroke symptoms), muscle weakness, and mental status changes secondary to hypertensive encephalopathy.

New associations between PA and clinical disease entities are emerging, particularly **AF** and **obstructive sleep apnea** (OSA).
A strong association between PA and AF has been observed in the past decade. Milliez et al. recently examined the rate of cardiovascular events in patients with PA and observed a 12-fold increased risk of AF in PA compared with EH (PA, 7.3; EH, 0.6; odds ratio, 12.1 ;(P,0.001). These results were confirmed by Monticone et al., who performed a systematic review and metaanalysis of 31 studies to examine the rates of cardiovascular events among participants with PA compared with EH. The risk of AF was **3.52** (95% CI, 2.06 to 5.99) in the participants with PA compared with EH.

Interestingly, the completeness of aldosterone blockade in PA may affect the future risk of developing AF.

Wolly et al recruited patients undergoing diagnostic evaluation for PA who had symptoms suggestive of OSA. The patients who had PA confirmed underwent polysomnography at baseline and at least 3 months after specific treatment for PA. Patients with aldosterone-secreting adenomas and BAH were treated with surgical adrenalectomy and MR blockade, respectively. For the patients who were diagnosed and subsequently treated for PA, the median apneahypopnea index dropped from 22.5 to 12.3 (P50.02).

These studies suggest a strong link between aldosterone excess, hypertension, and OSA, which can be effectively managed through aldosterone-reducing strategies.

MR Activation, Atherosclerosis, and Inflammation

The BP changes associated with high aldosterone states do not independently explain the tremendous burden of cardiovascular and renal disease within this population.

Although all of the mechanisms responsible for the increased risk of cardiovascular disease and renal disease remain undefined, inflammation and atherosclerosis are two putative factors that have been consistently identified.

Emerging research is elucidating novel mechanisms by which MR activation initiates a cascade of downstream events that culminate in vascular inflammation and progressive atherosclerosis.

MR activation appears to modulate conversion of monocyte/macrophage lineages to a more inflammatory phenotype. The beneficial effects of MR blockade on both inflammation and atherosclerosis further implicate MR activation as a causative pathway.

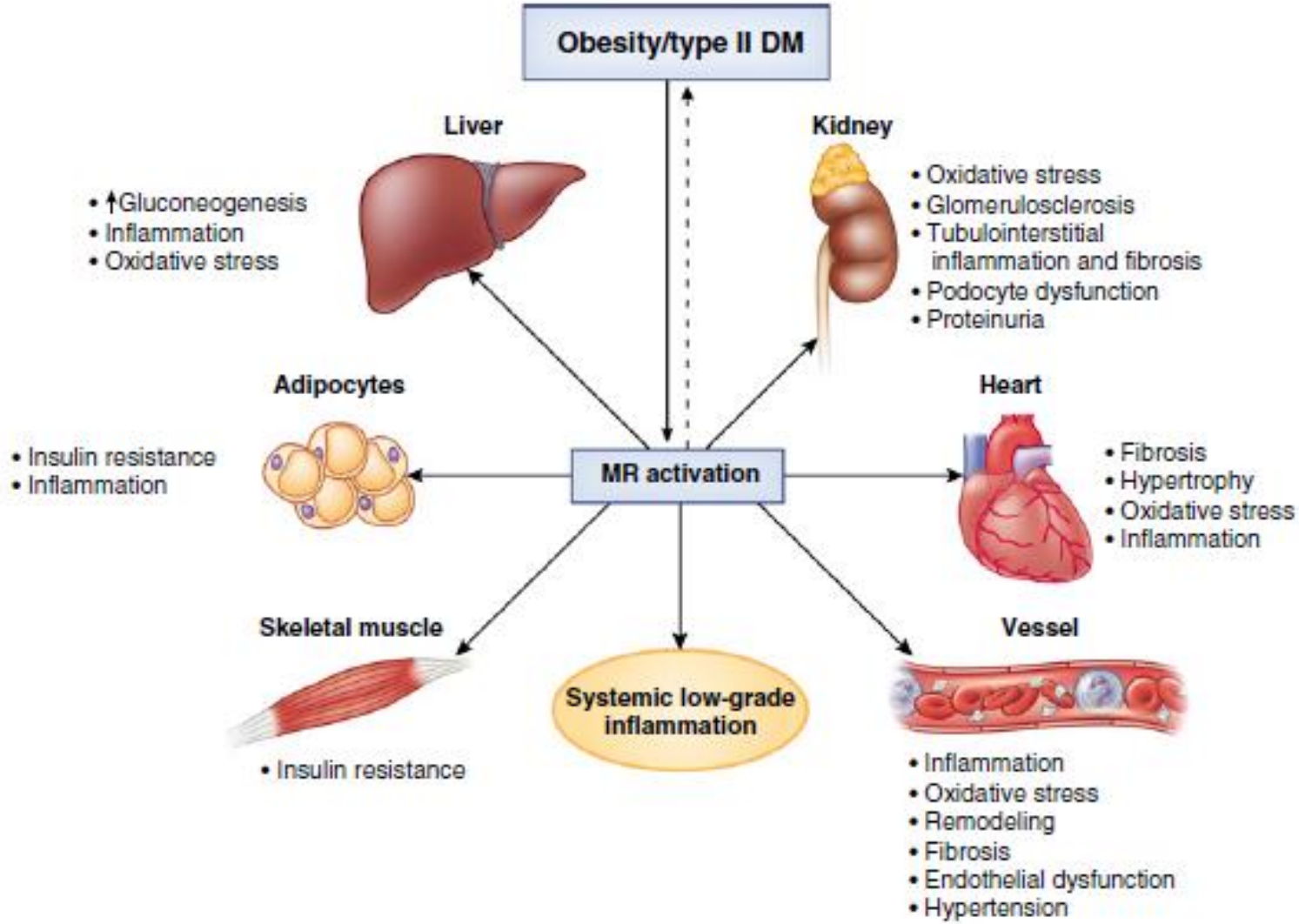


Figure 2. | The adverse consequences of mineralocorticoid receptor activation. DM, diabetes mellitus; MR, mineralocorticoid receptor.

Screening and Diagnosis

Patients meeting one of these criteria should be screened for PA:

- **Sustained BP >150/100 mm** Hg on each of three measurements obtained on different days.
- Hypertension (BP>140/90 mm Hg) **resistant to three conventional antihypertensive drugs (including a diuretic).**
- Controlled BP (<140/90 mm Hg) on **four or more antihypertensive drugs**.
- Hypertension and spontaneous or diuretic-induced **hypokalemia**.
- Hypertension and adrenal **incidentaloma**.
- Hypertension and **sleep apnea.**
- Hypertension and a **family history of early onset hypertension or cerebrovascular accident** at a young age **(<40** years).
- **All hypertensive first-degree relatives** of patients with PA.

Any patient with one or more of these criteria should be screened initially with the aldosterone-to-renin ratio (**ARR**), regarded as the gold standard and most reliable screening test for PA. However, due to several reasons, the ARR should be interpreted in the context of the plasma aldosterone concentration and plasma renin activity (PRA) or plasma direct renin concentration (DRC).

Inappropriately low renin may lead to an artificially elevated ARR. The ARR also may be affected by any changes caused by physiological factors that can affect the renin-angiotensin-aldosterone system.

If the ratio of **morning aldosterone to plasma renin activity is higher than 20 to 1**; then the excess aldosterone can be attributed to the adrenal gland as the primary source. Next, any of the **four confirmatory tests** may follow: 1) **oral sodium loading** 2) **saline infusion** 3) **fludrocortisone suppression** 4) **captopril challenge**, should suppress aldosterone; however, in a patient with primary aldosteronism, there will be a lack of aldosterone suppression.

Once primary aldosteronism is confirmed all suspected patients are recommended to undergo Adrenal **computed tomography scan** as the initial study and to exclude possible adrenocortical carcinoma. It is then recommended for the patient to have an **adrenal venous sampling**.

Confirmatory Testing

Clinical practice guidelines generally favor confirmatory testing for a positive ARR before subtype classification.

These tests are cumbersome,time consuming,and guidelines provide limited insight to the preferred confirmatory test.

Confirmatory testing does not appear to be an evidencebased practice.

In the recently published Aldosterone-Renin Ratio for Primary Hyperaldosteronism (AQUARR) study,the value of confirmatory testing for the diagnosis of PA was examined.

The study revealed three key findings that are applicable to this discussion. First, the study showed no diagnostic gain from the systematic use of the captopril challenge test over baseline ARR in a population with high prevalence of PA. Secondly, the sensitivity and specificity of ARR was validated in a population with high prevalence of PA. Lastly, ARR provided essential quantitative information in the evaluation of PA, that is to say, progressively increasing ARR values implied an exponential increase in specificity and decrease in false positive rates. Both the diagnostic odds ratio and the positive likelihood ratio were high (6.35 and 17.7, respectively) for ARR values>50. Taken together, these results imply that ARR is a highly effective screening test for PA and, even more surprisingly, an **ARR value>50 carried the same diagnostic power as confirmatory testing.**

The Endocrine Society guidelines for PA state that confirmatory testing can only be bypassed in patients with concomitant **hypokalemia, marked suppression of renin,and plasma aldosterone concentration (PAC) >20 ng/dl.**

Because hypokalemia occurs in only a minority of patients with PA, it is not surprising that only a very small percentage of patients would fulfill these criteria.

Given the poor performance of confirmatory testing in clinical studies, broadscale application of confirmatory testing in the evaluation of PA appears misguided.

Diagnostic work-ups of PA employ one or more of the following approaches:

- Oral sodium loading test. Patient is advised to increase sodium intake to about 6 grams (>200 mmol) for 3 days after which a 24-hour urine sodium and urine aldosterone is measured. A urinary aldosterone <10 µg/24 h (28 nmol/d) makes PA unlikely. An elevated urinary aldosterone >12 µg/24 h (>33 nmol/d) makes PA highly likely. This test is not recommended in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
- Saline infusion test. Patient stays in a recumbent position an hour before and during the infusion of 2 liters of 0.9% saline over 4 hours in the morning. Renin, aldosterone, cortisol, and potassium are drawn at time 0 and after 4 hours. BP and heart rate are monitored throughout the test. A post infusion aldosterone <5 ng/dL (140 pmol/L) makes PA less likely and levels >10 ng/dL (280 nmol/L) makes PA more likely. Values between 5-10 ng/dL are intermediate. This test is also contraindicated in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.

- Fludrocortisone suppression test. Patient is given 0.1 mg of oral fludrocortisone every 6 hours for 4 days, potassium chloride supplements to keep plasma potassium close to 4.0 mmol/L, and high sodium diet to maintain urinary sodium excretion rate of at least 3 mmol/Kg body weight. On the fourth day, plasma aldosterone and PRA are measured at 10 a.m. and plasma cortisol at 7 a.m. and 10 a.m. Plasma aldosterone >6 ng/dL (170 nmol/L) on day 4 at 10 a.m. confirms PA provided PRA is <1 ng/mL/h and 10 a.m. plasma cortisol is lower than the 7 a.m. measurement.
- Captopril challenge test. Patient is given 25–50 mg of captopril orally after sitting or standing for at least 1 hour. PRA, plasma aldosterone, and cortisol are measured at time 0, and at 1 or 2 hours after the challenge, with the patient remaining seated during this period. Plasma aldosterone is normally suppressed by captopril but remains elevated while PRA remains suppressed in patients with PA. False negatives have been reported in patients with APA and in those with IAH.

Normal Aldosterone

PA can occur in the setting of relatively normal PAC .There are a few plausible explanations for this paradoxic phenomenon.
Aldosterone is secreted in a pulsative manner that generally occurs more readily in the early morning.

If PAC samples are obtained during a latent phase, this will result in spuriously normal aldosterone levels.
Normal aldosterone levels in the setting of PA also result from a strong physiologic response to high sodium intake.
PAC levels can be normal despite a clinical phenotype of PA due to variation in aldosterone sensitivity.
Age and race appear to be major determinants of sensitivity to aldosterone.
Tu et al. found that the effect of aldosterone on BP intensified as age increased, especially in black individuals (P,0.01), suggesting an increased aldosterone sensitivity with age. In comparison to black people, age-related changes in aldosterone sensitivity in white individuals were not statistically significant.
These findings raise concern about using the absolute value of PAC as an inclusion criterion for PA.

Imaging for PHA Classification

The majority of guidelines on PA recommend computerized tomography (CT) or magnetic resonance imaging (MRI) as the best initial test for subtype classification in PA. These imaging modalities are an attractive option for subtype classification in PA compared with adrenal vein sampling (AVS) because they are generally safe, widely available, and can provide results expediently.unfortunately,the diagnostic performance of cross-sectional imaging for PA demonstrates wide variation and can serve as a barrier to curative adrenalectomy in suitable candidates.

CT and MRI have been increasingly used to detect adenomas,despite numerous studies challenging the accuracy of cross-sectional imaging.

In a systematic review, Kempers et al. found that CT/MRI results did not agree with AVS results in 38% of patients. More specifically, if only CT/MRI results had been used to determine lateralization of an adrenal abnormality, inappropriate adrenalectomy would have occurred in 15% of patients (where AVS showed a bilateral problem), inappropriate exclusion from adrenalectomy would have occurred in 19% (where AVS showed unilateral secretion), and adrenalectomy on the wrong side would have occurred in 4% (where AVS showed aldosterone secretion on the contralateral side).

In a more current study from Munich, in 175,patients who underwent unilateral laparoscopic adrenalectomy for PA after CT/MRI and lateralization by AVS, CT imaging and MRI showed discordant results of 39% and 41%, respectively.

These studies highlight the dangers of using CT or MRI to both diagnose and manage PA.

Imaging may have better reliability for the diagnosis of BAH rather than discrete adrenal adenomas. Lingam et al. found that the adrenal glands in patients with BAH were significantly (P,0.05) larger than those in patients with APA or in healthy control subjects. A sensitivity of 100% was achieved when a mean limb width of 3mmwas used to diagnose BAH, and a specificity of 100% was achieved when the mean limb width was 5 mm. In the future, broad application of limb width measurement of the adrenal glands may be a reliable and accurate tool for the diagnosis of BAH.

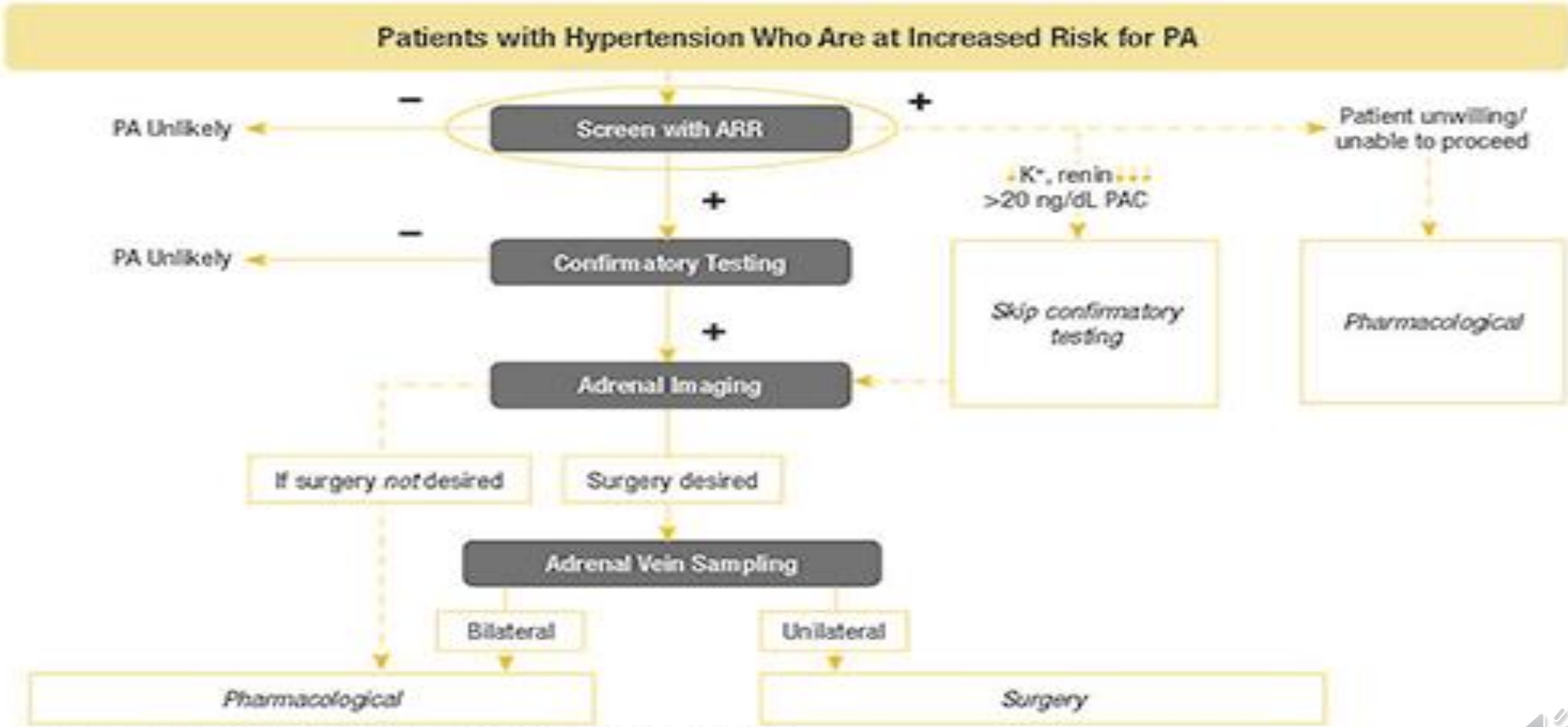
- **AVS**

AVS has widely been considered the **gold-standard test for subtype classification** in PA. The current clinical practice guidelines advocate use of AVS with measurement of plasma cortisol concentration and PAC.
Numerous studies have demonstrated the **superiority of AVS over imaging for subtyping of PHA**.despite these recommendations the use of AVS for subtype classification remains low.

The **best diagnostic test involves the measurement of cortisol and aldosterone in bilateral adrenal venous effluent and a peripheral vein before and during an ACTH infusion. Cortisol will be used to evaluate the catheter placement in the adrenal veins**, as levels from the two sides should be similar. **When an adenoma is present, the aldosterone-to-cortisol ratio on one side is usually at least five times greater** than the other indicating suppression. Bilateral hyperplasia tends to produce similar values on each side.

- If the study points towards a **unilateral adenoma**, **then laparoscopic adrenalectomy** is the preferred treatment. If the patient declines surgery or is not a surgical candidate, medical therapy is the recommended route. If the study points towards a bilateral cause, then medical treatment with a mineralocorticoid antagonist is warranted.

F1 Endocrine Society recommended diagnostic algorithm for primary aldosteronism (modified from *1*).



Abbreviations: Plasma Aldosterone Concentration, PAC; Aldosterone-to-Renin Ratio, ARR

Which drugs should with held previousARR test

Spironolactone and **diuretics** should be withheld for **6 weeks** before testing.

-If necessary to **maintain hypertension control, patients should be treated with other antihypertensive medications that have lesser effects on the ARR (ie, verapamil slow-release, hydralazine [with verapamil slow-release, to avoid reflex tachycardia], prazosin, doxazosin, terazosin).** It is a shared opinion **that dihydropyridinic calcium channel blockers do not significantly affect aldosterone secretion**, causing mainly an **increase in PRA**, which rarely gives false negatives.

-**Beta-blockers, ACE inhibitors, selective-serotonin reuptake inhibitors, and oral contraceptives** have been shown to influence the results of the test. Ideal testing conditions involve discontinuation of such medications **2 weeks** prior.

-Patients should also eliminate products derived from the **licorice root** because these can interfere with **11beta-hydroxysteroid dehydrogenase**, producing a state of apparent mineralocorticoid excess.

-**Renal impairment can lead to a high ARR** in patients without primary hyperaldosteronism because fluid retention suppresses PRA and hyperkalemia stimulates aldosterone secretion.

• Treatment / Management

Treatment for primary hyperaldosteronism includes laparoscopic resection for adenomas. This procedure will usually resolve the hypokalemia, but **hypertension can persist in up to 65% of patients post adrenalectomy.**

Surgery is the preferred treatment for patients with unilateral aldosterone-producing adenoma. After unilateral adrenalectomy, almost all patients have the resolution of hypokalemia and moderate improvement in blood pressure control.

In those who are **unable to undergo surgery or have bilateral adrenal hyperplasia, mineralocorticoid antagonists** such as spironolactone or eplerenone are an option.

In a randomized study, the antihypertensive effects between spironolactone and eplerenone in patients with primary hyperaldosteronism were studied showing that spironolactone was more effective than eplerenone in controlling blood pressure.Amiloride, a sodium channel blocker, may be helpful in the treatment and other antihypertensive agents can be continued as needed to optimize blood pressure control. **Spironolactone is considered the first line agent for patients who cannot undergo surgical resection**.

• Innovative Medical Therapy

Several important advances in medical therapy over the last few years may have therapeutic implications for PA in the near future. One such advance is the advent of a novel class of drugs called **nonsteroidal MRAs.** Several drugs in this class are under development, including **apararenone**, **finerenone**, and **esaxerenone**.
Esaxerernone has recently received marketing approval in Japan for the treatment of hypertension based on positive results of phase 3 trials.
Nonsteroidal MRAs tend to **have greater receptor selectivity compared with spironolactone**, and **stronger MR binding affinity than eplerenone** .These new classes of drugs tend to have **improved side effect profiles despite improved potency** Additionally, **nonsteroidal MRAs** have a **lower risk of hyperkalemia** than traditional MRAs.

This may afford the opportunity **to safely combine angiotensin-converting enzyme inhibitors or angiotensin receptor blockers** with nonsteroidal MRAs for a more complete aldosterone receptor inactivation in PA, without subsequent risk of hyperkalemia.
These agents will greatly expand the armamentarium of available medical therapy for PA, particularly in patients with BAH and APA who are not candidates for surgical adrenalectomy.

- **Primary hyperaldosteronism in pregnancy**

As **aldosterone and renin are physiologically increased during pregnancy** and confirmation tests are not recommended, the **diagnosis of PA during pregnancy relies on a repeatedly suppressed plasma renin level.**

Mineralocorticoid receptor antagonists (MRAs) are the most effective drugs to treat hypertension and hypokalemia in patients with PA. However, spironolactone (FDA pregnancy category C) might lead to undervirilization of male infants due to the anti-androgenic effects. Although data in the literature are very limited,treatment with spironolactone is not recommended.

Eplerenone (FDA pregnancy category B) is a selective MRA without anti-androgenic potential.

If MRA treatment is required in pregnancy, eplerenone appears to be a safe and effective alternative, although symptomatic treatment with **approved antihypertensive drugs and supplementation with potassium is the first choice**.

In case of aldosterone-producing adenoma, laparoscopic adrenalectomy is a therapeutic option in the second trimester of pregnancy.

از توجه شما متشکرم