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Discussion About The New Endocrine Society Practice Guidelines About Primary Aldosteronism(pa) from 2025

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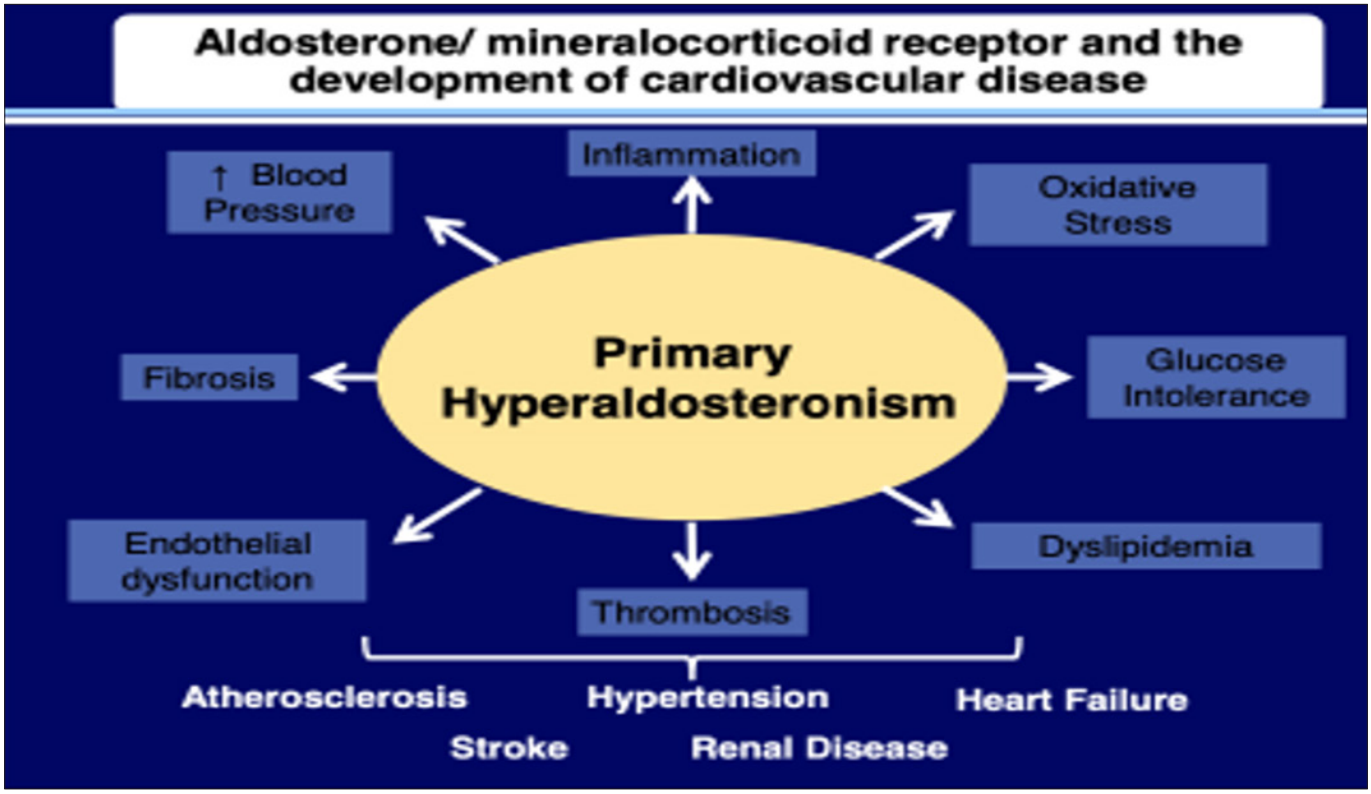
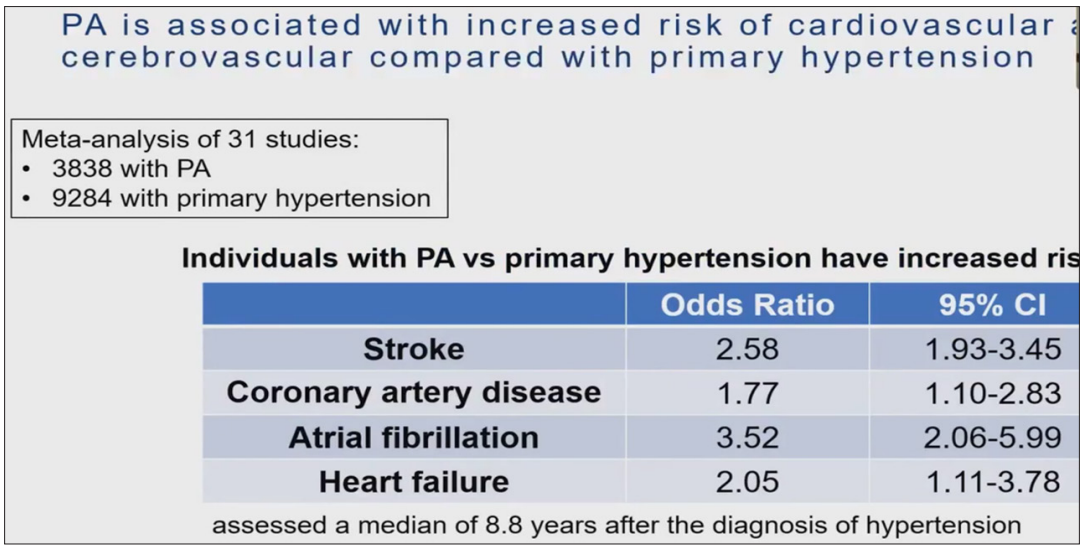
The Recommendation Number One[1,2] : In all patients with Hypertension consider checking for primary Hyperaldosteronism by checking plasma aldosterone, Plasma renin activity or concentration, plasma aldosterone/ plasma renin activity/concentration ratio. Potassium should be checked also because low Potassium leads to low aldosterone and the aldosterone level should be rechecked after Potassium is repleted.



The reason for this recommendation is that the excess of aldosterone as depicted above leads to fibrosis, inflammation, endothelial dysfunction, Hypertension (HTN), Hyperglycemia, Dyslipidemia and thrombosis. Screening all HTN patients and treating it if Primary hyperaldosteronism(PA) is found decreases morbidity/mortality and is cost effective. The prevalence of PA is 10-25% in patients with HTN!



As we can see from the slide above having HTN due to hyperaldosteronism increases the risk of coronary artery disease, Atrial fibrillation, hear failure and stroke 1.77- 3.52 times more than having essential HTN. It also increases albuminuria and proteinuria two times[3-4].

Recommendation Number 2[5,6,7] : In individuals with HTN and Primary aldosteronism(PA)it is suggested PAspecific therapy(surgical or medical.

Adrenalectomy for lateralizing PA leads to:

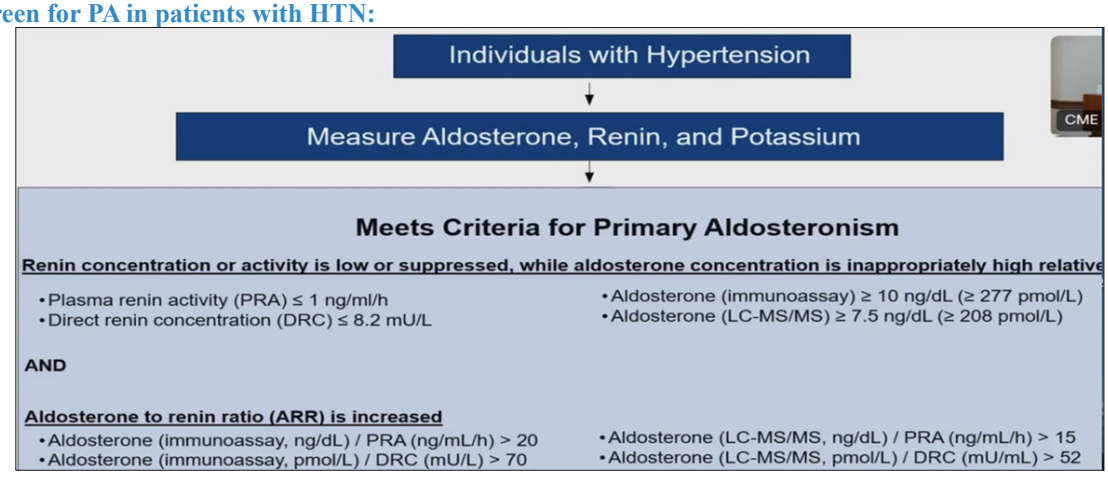
- Biochemical resolution of PA in many
  Normalization of K, renin and aldosterone
- Improved BP control or normalization of BP in many
- ↓ rates of CV and cerebrovascular events

MR antagonist therapy leads to:

- Improved BP control
- Resolution of hypokalemia
- Improved CV risk

As we can see from the slide above treatment of hyperaldosteronism with adrenalectomy or mineralocorticoid receptor antagonists(MRA) and normalization of potassium, renin and aldosterone decreases blood pressure and the incidence of cardiovascular events!

How to screen for PA in patients with HTN:



Starting MRA in PA

- With MRA intiation, consider hypertension severity and stop/reduce other anti-hypertensives
- Stop K supplements within 2-4 days of MRA initiation unless severely hypokalemic
- Recommend low sodium diet

Recommendation 3 [1,8]

In individuals with hypertension, we suggest primary aldosteronism (PA) screening with serum/plasma aldosterone concentration and plasma renin (concentration or activity).

Technical Remarks

Screen for PA by measuring serum/plasma aldosterone and plasma renin (concentration or activity) in the morning with individuals seated and avoiding dietary sodium restriction during the few days

Prior to Screening: Potassium should be measured alongside **Renin and aldosterone**—not for screening itself but to aid in accurate interpretation of aldosterone—as low potassium may lead to a falsely low aldosterone

If screening results are negative and the patient has hypokalemia, potassium should be corrected to within the laboratory reference range and screening should be repeated

.

In figure 1 bellow is described what needs to be done if there are concerns for False positive and False negative results

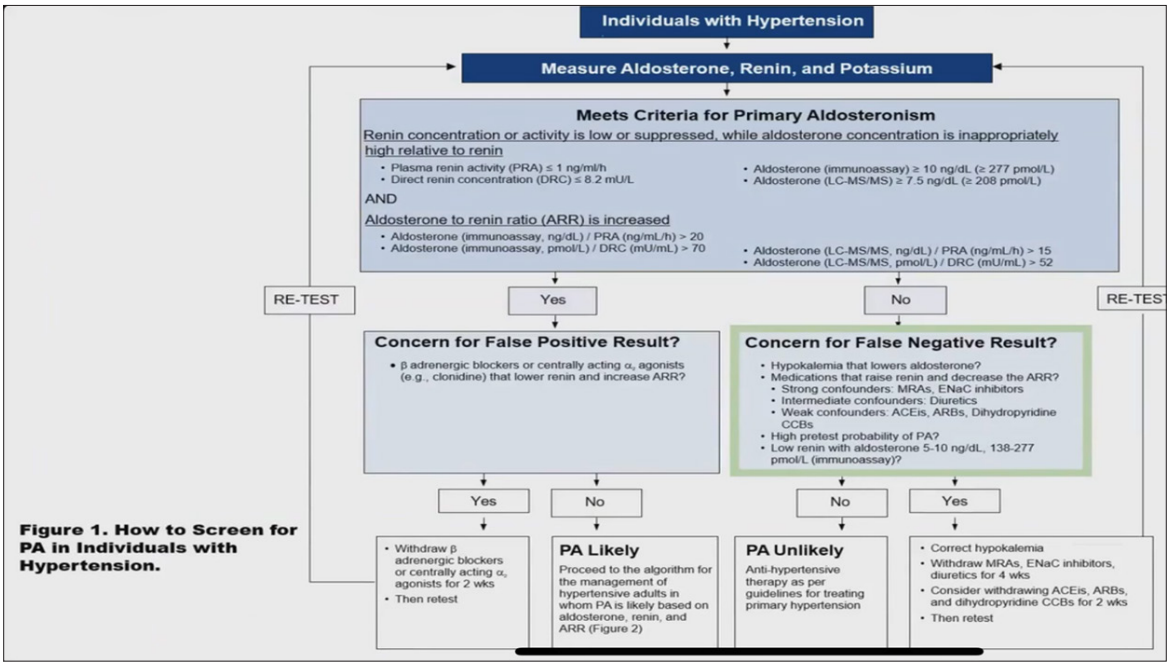
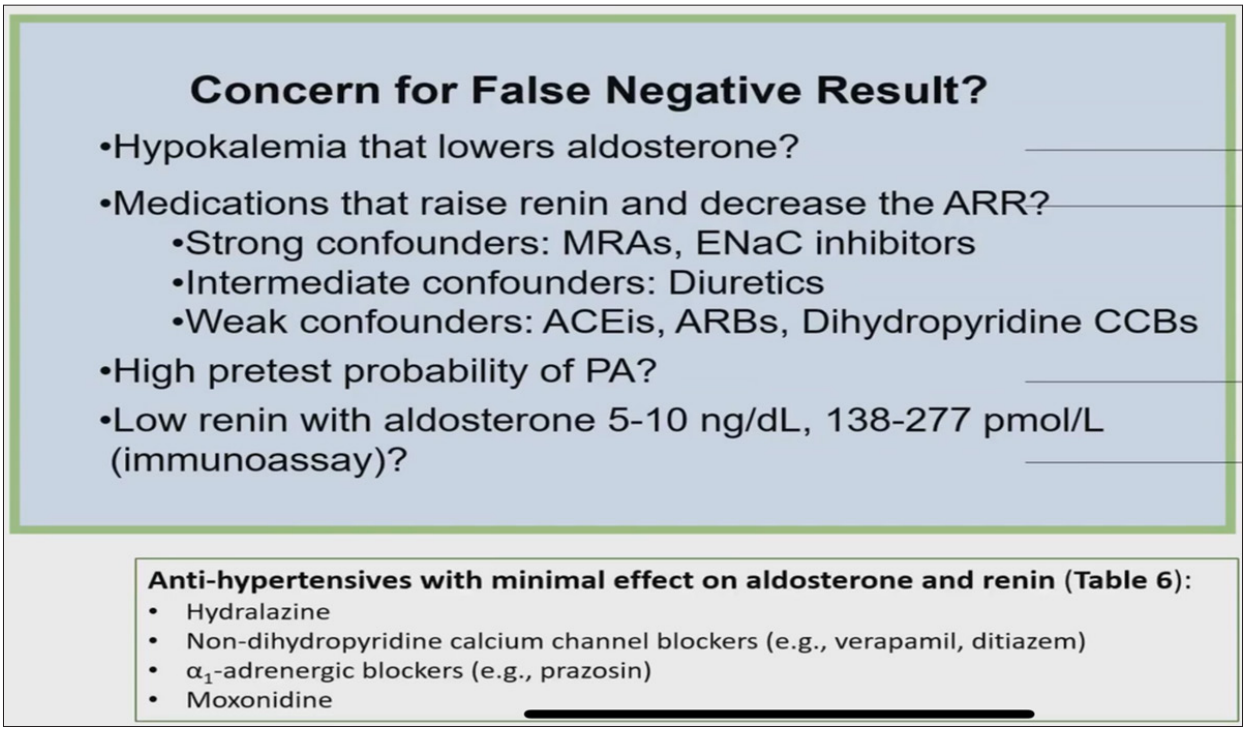


Figure 1. How to Screen for PA in Individuals with Hypertension.



The aldosterone, renin, and ARR values above are provided for guidance. However, as with many diagnostic tests based on continuous variables, the sensitivity and specificity depend on the selected threshold. Aldosterone and renin levels are further influenced by individual variability, local laboratory assays, and other factors. Where possible, clinicians should rely on local laboratory cut points, as assays may vary. No cut point is perfect—each carries a trade-off between false positives and false negatives. Therefore, results should be interpreted within the context of the patient's pretest probability for PA, along with potential interfering medications and conditions.

If the individual's initial screen is negative and factors are present that could have led to a false-negative result (eg, hypokalemia or medications), the test should be repeated on a different day, preferably after correcting hypokalemia (where present) and withdrawing interfering medications if safe and feasible (for 4 weeks for mineralocorticoid receptor antagonists [MRAs], epithelial sodium-channel [ENaC] inhibitors [eg, amiloride, triamterene], and other diuretics; and 2 weeks for angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]), which raise renin or lower aldosterone. For the most accurate determination of potassium, measure plasma potassium in blood collected slowly with a syringe and needle

(preferably not using a vacuum-sealed blood collection tube to minimize the risk of spuriously raising potassium). During collection, avoid fist clenching, wait at least 5 seconds after tourniquet release (if used) to achieve insertion of needle, and ensure separation of plasma from cells within 30 minutes of collection.

If the individual's initial screen is positive, but they are receiving medications (eg, β-adrenergic blockers and centrally acting α2-agonists [eg, clonidine, α-methyldopa]) that can lower renin and thereby cause false-positive results, the test should be repeated after withdrawing those medications for 2 weeks if it is safe and feasible. Consider potential false positives induced by β-adrenergic blockers when aldosterone is 10 to 15 ng/dL (277-416 pmol/L) by immunoassay or 7.5 to 10 ng/dL (208-277 pmol/L) by LC-MS/MS; if aldosterone is above these concentrations, PA is likely despite being on β-adrenergic blockers.

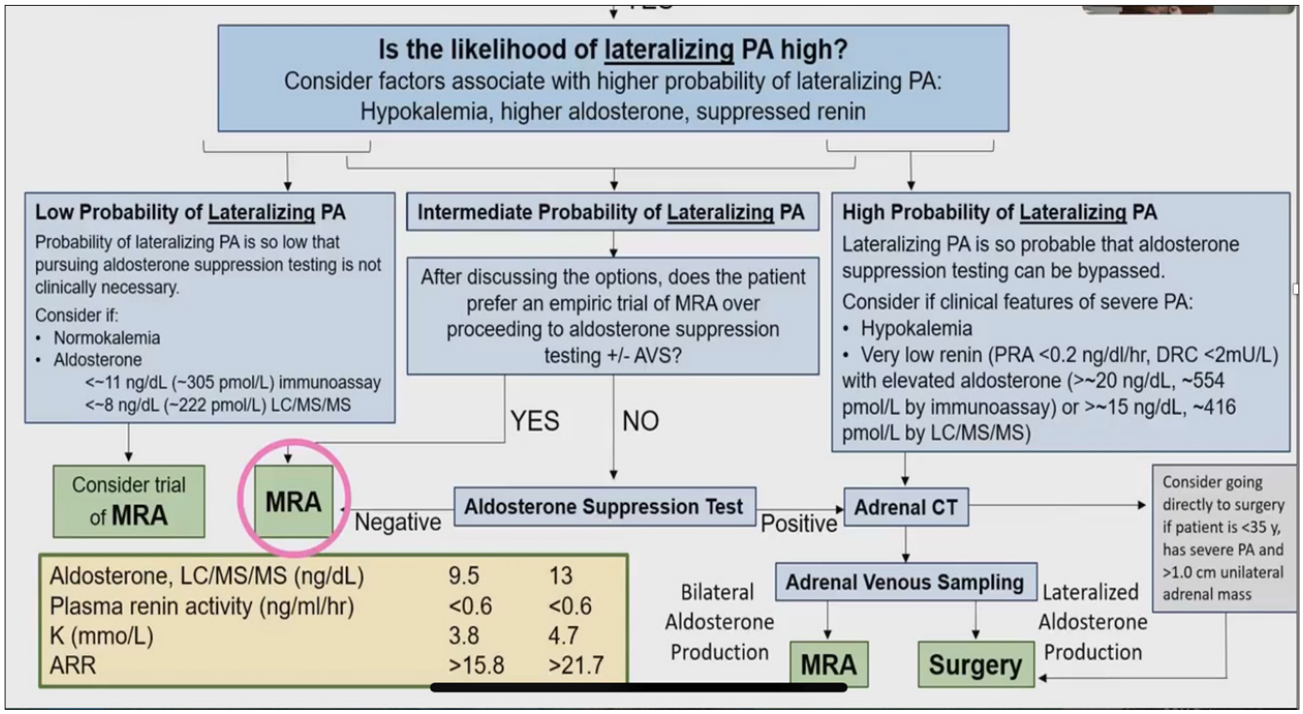
If screening hypertensive patients with chronic kidney disease, renin decreases proportionately to nephron loss, except in cases where there is renal ischemia from renal artery stenosis where renin will be elevated. Aldosterone can also be elevated in chronic kidney disease, leading to overall increases in false-positive testing. If the patient is on MRA and renin is suppressed and aldosterone is high the screening is valid for PA and MRA antagonist should not ne stopped for 4 weeks and the test repeated.

If all initial screening is negative, consider re-screening in the future if a patient develops:

- Unexplained worsening of hypertension or resistant hypertension
- New spontaneous or diuretic-induced hypokalemia
- Atrial fibrillation in the absence of structural heart disease or hyperthyroidism

Recommendation Number 4 [1]

In individuals who screen positive for primary aldosteronism (PA), the suggestion is to perform aldosterone suppression testing in situations when screening results suggest an intermediate probability for lateralizing PA and individualized decision making confirms a desire to pursue eligibility for surgical therapy. Compare to previous guidelines aldosterone suppression test in not recommended to confirm PA in almost everyone who screens positive fot the disease. Aldosterone suppression test in USA is usually done by using salt suppression- tablets as outpatients or 0.9% Sodium chloride as in patient.



As we can see compare to the previous recommendation's confirmation of PA with aldosterone suppression test to confirm PA is done only in Intermediate probability for the disease patients. In high probability for lateralization patients adrenal CT is done followed usually by adrenal venous sampling(AVS) and surgery in unilateral disease or mineralocorticoid antagonists(MRA) treatment in bilateral disease. In low probability for lateralization patients a trial with MRA is done and if not successful only then aldosterone suppression test is considered.

Recommendation 5 [1,5,6,7]

In individuals with primary aldosteronism (PA), it is suggested medical therapy with MRA or surgical therapy with the choice of therapy based on lateralization of aldosterone hypersecretion and candidacy for surgery Technical remarks:

- Surgical therapy by total unilateral adrenalectomy, usually by the laparoscopic approach, is mainly offered to individuals with lateralizing PA who choose to pursue the surgical option.
- Lifelong medical therapy that includes a mineralocorticoid receptor antagonist (MRA) is usually offered to individuals

with bilateral PA or lateralization status unknown and to those who are not surgical candidates or who decline the surgical option.

- Individuals with mild PA typically have bilateral disease and may bypass adrenal venous sampling (AVS), proceeding directly to medical management, as outlined in the diagnostic algorithm described above
- Individuals with multiple comorbidities who may not be good surgical candidates may also proceed directly to medical therapy with MRA

Recommendation 6[1]

In individuals with primary aldosteronism (PA) considering surgery, it is suggested adrenal lateralization with computed tomography (CT) scanning and adrenal venous sampling (AVS) prior to deciding the treatment approach (medical or surgical)

Technical Remarks

- Individuals with PA who desire and are candidates for adrenalectomy should undergo AVS in order to reliably differentiate lateralizing from bilateral forms.
- A potential exception is when the diagnosis of unilateral aldosterone-producing adenoma (APA) is so likely that AVS could be considered unnecessary (eg, individual age <35 years with marked PA with hypokalemia and a > 1.0-cm unilateral adrenal adenoma on CT scanning).

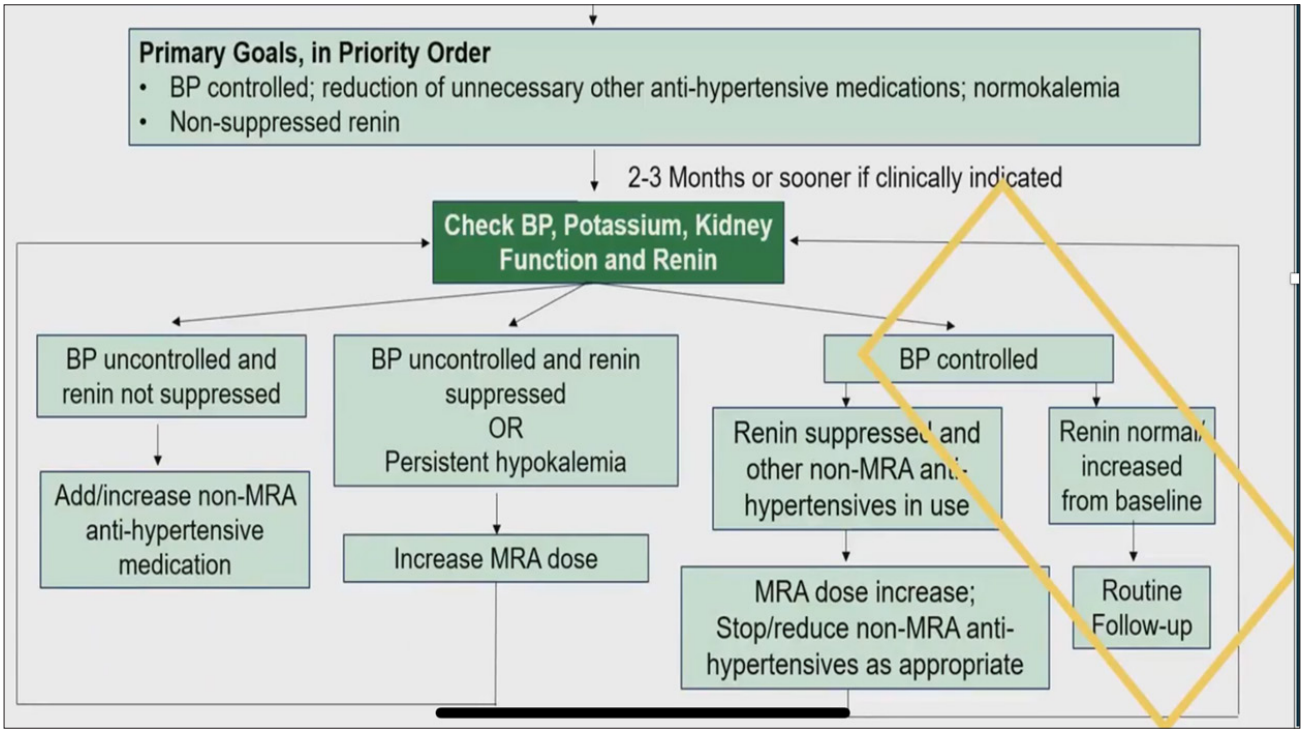
New developments for lateralization in patients with PA besides Adrenal venous sampling(AVS).

1. AVS is very invasive procedure and in up to 25% of the cases the right adrenal artery cannot be appropriately cannulated.
2. The new although still not recommended and experimental procedure for lateralization of PA is 11C-metomidate positron emission tomography-computed tomography (11C-MTO PET-CT). The procedure is non invasive and although still investigational holds great expectation as alternative to the current gold standard for lateralization of PA - AVS.

Recommendation Number 7[1]

In individuals with PA receiving PA specific therapy in whom the renin is suppressed and the blood pressure(BP) is not controlled it is suggested increasing the dose of PA specific therapy to raise the renin.

This recommendation applies to individuals with PA receiving aldosterone-directed medical therapy whose blood pressure (BP) remains high. Uncertainty remains as to whether titrating aldosterone-directed medical therapy to raise renin when BP is controlled is efficacious. The panel does not specify a renin level to target but rather advises titration of aldosterone-directed medical therapy to a rise in renin from pretreatment baseline.



As we can see from the slide above if the renin is non suppressed but the BP is not controled we should add or increase the dose of non- MRA anti NTN medications.

In the situations in which the BP is controlled but renin is suppressed we should increase the dose of MRA medications and stop or reduce the dose of non MRA anti- HTN medications.

The goal is normal/ increased from baseline renin and control of the BP.

Recommendation 8[1]

In individuals with primary aldosteronism (PA) and adrenal adenoma, it is suggested a dexamethasone suppression test

Technical Remarks

- A dexamethasone suppression test should be performed, and a positive test should prompt further evaluation for Cushing syndrome as detailed in the Endocrine Society Clinical Practice Guidelines.
- For the 1-mg overnight dexamethasone suppression test, 1 mg dexamethasone is taken orally at 23:00 to 24:00 with serum cortisol measured at 08:00 to 09:00 the next morning. A serum cortisol >1.8 µg/dL (50 nmol/L) suggests autonomous cortisol secretion (ACS).
- For individuals with mild autonomous cortisol secretion, measuring plasma metanephrine during adrenal venous sampling may help lateralize both aldosterone and cortisol secretion, although further research is needed. It will also be important to measure early morning cortisol following adrenal surgery and prepare for a period of possible glucocorticoid insufficiency.

The recommendation number 8 comes from recent meta-analysis which has found Mid autonomous cortisol secretion(MACS) in 22% of patients with PA due to adrenal adenomas. MACS in this adenomas is linked to older age, larger adenomas and renal dysfunction but shows similar cardiometabolic profiles to aldosterone –only cases. Co- secretion might complicate the interpretation of AVS by suppressing the contralateral cortisol. Surgical outcomes are comparable between co-secretors and non- co-secretors.

Recommendation 9[1,6,7]

In individuals with primary aldosteronism (PA) receiving PA-specific medical therapy, the suggestion is to use spironolactone over other mineralocorticoid receptor antagonists (MRAs) due to its low cost and widespread availability

Technical Remarks

- The recommendation is driven by the availability and low cost of spironolactone vs other MRAs; however, all MRAs, when titrated to equivalent potencies, are anticipated to have similar efficacy in treating PA. MRAs with greater mineralocorticoid receptor specificity and fewer androgen/progesterone receptor-mediated side effects may be preferred.
- When initiating an MRA, consider hypertension severity for dosing and potential discontinuation of other antihypertensive medications
- Monitor potassium, renal function, renin (concentration or activity), and blood pressure response during follow-up to guide MRA dose titration.

After initiation of Spironolactone frequently the GFR decreases and creatinine in the serum increases. This is expected response because PA is the state of hyperfiltration in the kidneys and blocking the effect of excess aldosterone leads to these hemodynamic changes.

Recommendation 10[1,6,7]

For individuals with primary aldosteronism (PA) receiving PA-specific medical therapy, it is suggested to be used mineralocorticoid receptor antagonists (MRAs) rather than epithelial sodium-channel (ENaC) inhibitors (amiloride, triamterene).

Clinicians may start at a relatively low dose MRA (spironolactone 12.5-25 mg/d or eplerenone 25 mg daily or twice daily). Medically complex or frail individuals and those in whom MRA–drug interactions (eg, with an ACE inhibitor or ARB) are possible may need careful monitoring. For individuals with more severe PA, especially if profound hypokalemia is present, a higher initial dose could be considered (spironolactone 50 mg/d or eplerenone 50 mg twice daily).

All individuals should get routine measurement of serum electrolytes, renal function, and renin within 2 to 3 months of starting MRA therapy; more frequent serial measurements may be needed in those with prior severe hypokalemia or renal impairment. Some experts recommend enquiring about dietary sodium or measuring 24-hour urine sodium at baseline and periodically throughout follow-up as a means of tracking dietary salt restriction; a target of <85.5 mmol/d sodium is recommended (representing <5 g/d salt intake)

MRA dose changes to target BP control should occur at 8- to 12-week intervals, and the full drug effect may take up to 3 months in more severe PA forms. Typical doses required to de-suppress renin are variable and likely higher than doses used as empiric add-on for resistant hypertension[1]; most individuals will achieve renin de-suppression with spironolactone doses (or spironolactone dose equivalents) between 50 and 100 mg/day. Spironolactone may be increased in 25- to 50-mg increments, and eplerenone in 25- to 100-mg increments. With each MRA dose change, repeat electrolytes, renal function, and renin 2 to 3 months later is recommended. When possible, consider off-titration of other anti-hypertensives. Once renin is de-suppressed, and if further BP reduction is required, other non-MRA antihypertensives should be added or up titrated. If blood pressure is controlled on MRA monotherapy, there is insufficient evidence to suggest further MRA dose increases in response to low renin levels alone

Normalization of serum potassium usually occurs, even with lower-dose MRAs, in the first 3 to 5 days, so it is reasonable to reduce or discontinue any potassium supplements at day 2 to 4 of MRA initiation in all but the most severe hypokalemic cases. Individuals who do require ongoing potassium supplementation require frequent careful monitoring of potassium. Dietary salt restriction is a critical part of determining response to MRA therapy); individuals should be explicitly instructed on and assisted with dietary salt reduction strategies. An ongoing high-salt diet is a very common reason for apparent nonresponse to MRA therapy.

Routine follow-up after MRA dose optimization should generally consist of blood pressure monitoring, along with

annual measures of potassium and kidney function. Patients with chronic kidney disease or other risk factors for impaired renal function/electrolyte disorders (eg, combination MRA and ACE inhibitor/ARB drugs) should undergo biochemical monitoring more frequently. Routine repeat renin measures are not necessary unless re-entering the MRA titration algorithm due to incomplete BP/potassium control.

Gynecomastia from spironolactone is dose-related and may appear as early as 1 to 2 months into therapy but more commonly after ≥6 months of treatment. In some cases (especially in younger males) a dose reduction to ≤50 mg per day resolves gynecomastia. Some men may request a switch to a more selective MRA such as eplerenone or other new MRA agents; amiloride is an alternative option. This almost always allows complete resolution of the gynecomastia if it has not already progressed to advanced size. Some patients may want to avoid antiandrogen and antiprogesterone effect of spironolactone and use eplerenone from the beginning of the treatment.

Conclusion[1,9,10]

1. The guidelines suggest that all patients with HTN should be screened for PA.
2. The screening tests used is plasma/ serum aldosterone concentration and plasma renin activity or concentration.
3. Not almost all patients as per previous guidelines should undergo aldosterone suppression test.
4. Treatment focuses on the choice of medical versus surgical treatment of PA.
5. The patients who choose medical therapy should be treated with MRA preferably Spironolactone.
6. All patients with adenoma and PA should be screened with 1 mg Dexamethasone suppression test for cortisol co- secretion and MACS.
7. The diagnosis and treatment of PA is cost effective.

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