بسم الله الرحمن الرحیم

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 2453–2495

Presentation by : Dr. Amir Reza Goharian , ***Endocrinologist***

Member of Iranian Endocrine Society

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, 2453–2495
https://doi.org/10.1210/clinem/dgaf284
Advance access publication 14 July 2025

Clinical Practice Guideline

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

Importance

- A meta- analysis of 31 studies (3838 individuals with PA, 9284 with primary hypertension) demonstrated that individuals with PA have increased risk of *stroke* (odds ratio 2.58, 95% CI 1.93-3.45), *coronary artery disease* (odds ratio 1.77, 95% CI 1.10-2.83), *atrial fibrillation* (odds ratio 3.52, 95% CI 2.06-5.99), and *heart failure* (odds ratio 2.05, 95% CI 1.11-3.78) a median of 8.8 years after the diagnosis of hypertension (2).

Importance

- Another meta-analysis of 46 studies (6056 individuals with PA, 9733 with primary hypertension) found an increased risk of renal disease as evidenced by ***albuminuria*** (odds ratio 2.09, 95% CI 1.40-3.12) and ***proteinuria*** (odds ratio 2.68, 95% CI 1.89-3.79) (1).

- Furthermore, individuals with PA often report reduced psychological well-being and quality of life (3-5).

ESC - 2024

- The 2024 European Society of Cardiology (ESC) guidelines for the management of elevated BP and hypertension suggest screening for PA ***in all adults*** with diagnosed hypertension (6).

Wonderfull !!!!

- The GDP consisted of content experts representing the following clinical specialties: endocrinology, general internal medicine, genetics, ***hypertension specialists***, epidemiology, and a patient representative.

- This guideline will be reviewed ***annually*** to assess the state of the evidence and determine if any developments warrant an update to the guideline.

Question 1. Should care that includes primary aldosteronism screening be applied to all individuals with hypertension, compared with care without screening?

Recommendation 1

In all individuals with hypertension, we suggest screening for primary aldosteronism (PA) (2 | ⨁⨁OO).

In all individuals with hypertension, we suggest screening for primary aldosteronism (PA) (2 | ⨁⨁OO).

- This is a ***conditional recommendation***, with implementation depending on contextual factors such as available resources, local expertise, and healthcare system capacity, which may affect feasibility and prioritization.

Who Should be Screened for Primary Aldosteronism?

Background

1. Primary aldosteronism (PA) is the most common endocrine cause of secondary hypertension with an estimated prevalence of 5% to 14% of individuals with hypertension seen in primary care (34-36) and up to 30% in referral centers (37-39).

2. PA is particularly prevalent in individuals with specific clinical characteristics or comorbid conditions (Table 3).

Table 3. Prevalence of primary aldosteronism in different subgroups

Setting	Prevalence	Reference
Hypertension in Primary Care	5.9% (range, 3.2-14.0)	(34-36, 39)
Hypertension in referral centers	7.2% (range, 0.7-21.9)	(39)
Hypertension in young adults (ages 18-40 years)	16.2%	(39)
[a]Grade 1 hypertension	3.9%-15.7%	(23, 34)
[a]Grade 2 hypertension	9.7%-21.6%	(23, 34, 37)
[a]Grade 3 hypertension	11.9%-19%	(34, 37)
Resistant hypertension	11.3%-29.1%	(23, 40-42)
Hypertension and hypokalemia	28.1%	(43)
Hypertension and adrenal incidentaloma	4.4% (range, 0.4-24.6%)	(44)
Hypertension and atrial fibrillation[b]	42.5%	(45)
Hypertension and type 2 diabetes mellitus	11.3%-19.1%	(46, 47)

PA remains underdiagnosed : (eg.)

- The commissioned systematic review (53) identified a single retrospective observational study (51) that showed that screening for PA was associated with a significantly lower SBP over time.

- The authors reported that of **269 010 US veterans** with apparent treatment-resistant hypertension, only 1.6% were tested for PA with a concomitant measurement of blood aldosterone concentration and either plasma renin activity (PRA) or direct renin concentration (DRC).

PA remains underdiagnosed : (eg.)

- In a Canadian population of 1 million hypertensive individuals, fewer than 1% had been screened for PA (67),
- and an Australian primary care study reported that aldosterone was only measured 66 times over 1.5 million primary care patient encounters during a 16-year period (68).
- Similar rates of low detection have been observed in the United States and Europe (50, 51).

Certain challenges :

- The accuracy of screening tests : medication use, dietary sodium intake, and test conditions.
- The feasibility of universal screening
- costs and resources required,
- cost-effectiveness,
- acceptability, feasibility, and
- the potential impact on health equity.

Universal Screening for PA

- Screening for PA in the general hypertensive population has been shown to be cost-effective in health economic studies conducted in Japan, Australia, and China.
  - The favorable cost - effectiveness is largely driven by the reduction in long-term complications associated with untreated PA.

Justification for the Recommendation

- Despite these limitations, the panel judged that the potential benefits of early detection and specific treatment for PA likely outweigh potential harms, including false-positive results and unnecessary downstream testing.

- In making this decision, the panel placed high value on offering patients the opportunity for evaluation and identification of an endocrine etiology for hypertension—one that is treated differently from primary hypertension and that offers the possibility of cure in cases of lateralizing PA.

Justification for the Recommendation

- depending on available resources, local expertise, and healthcare system capacity.
- a number of individuals with low renin do not have PA (eg, individuals with high salt intake or Liddle syndrome),
- The recommendation is applicable to individuals older than age 16 years.
- Pediatric individuals should be considered to have a positive screening test at an ARR cutoff lower than for adults (78,79).

DDX

- The interpretation of aldosterone and renin levels and the ARR and subsequent management is also different in ***pregnant*** individuals due to pregnancy-related changes in the renin–angiotensin–aldosterone system (RAAS) (80, 81).

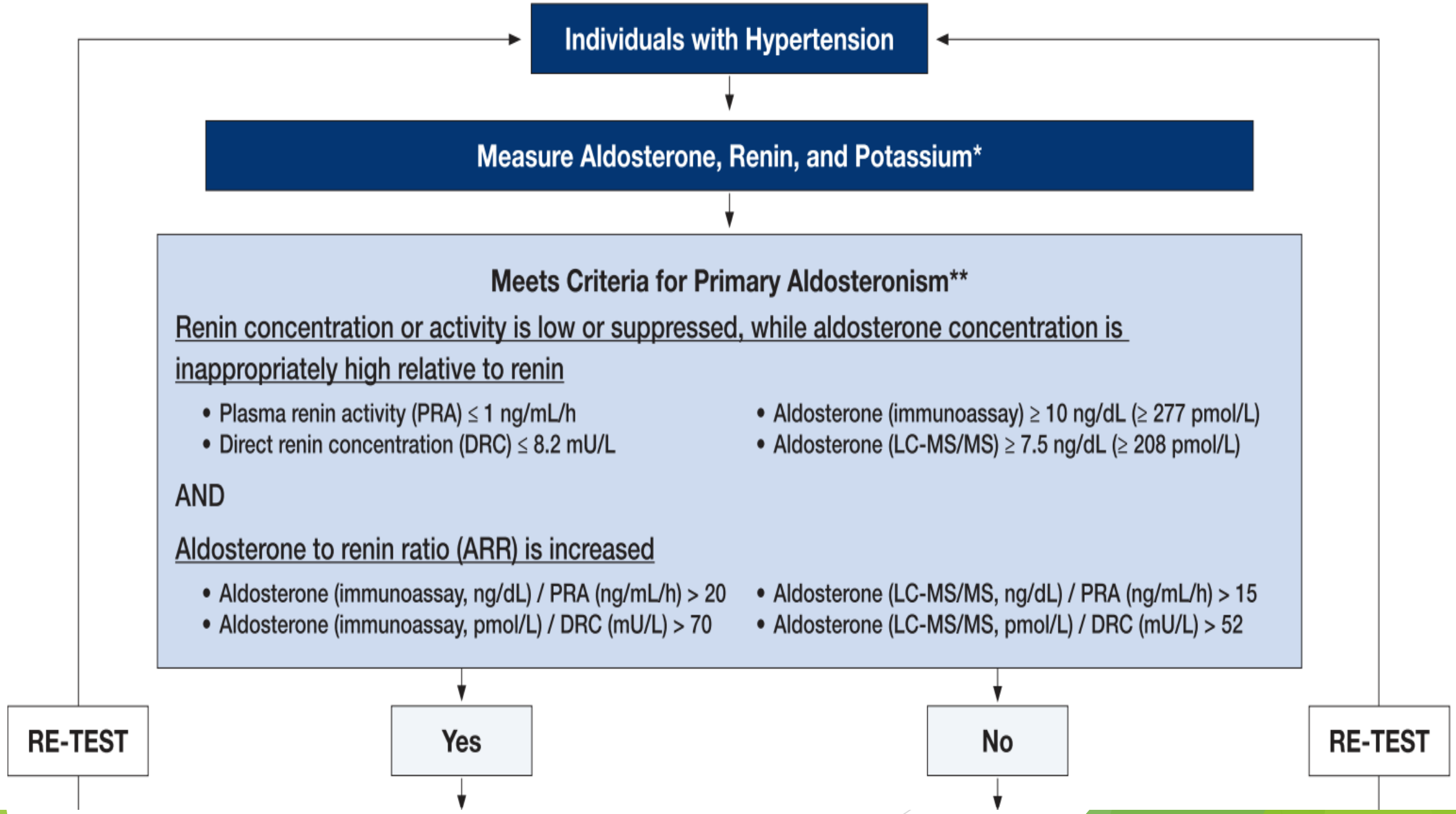
- Individuals with concomitant ***heart failure*** may have unsuppressed renin levels, and diagnosis requires expert input.

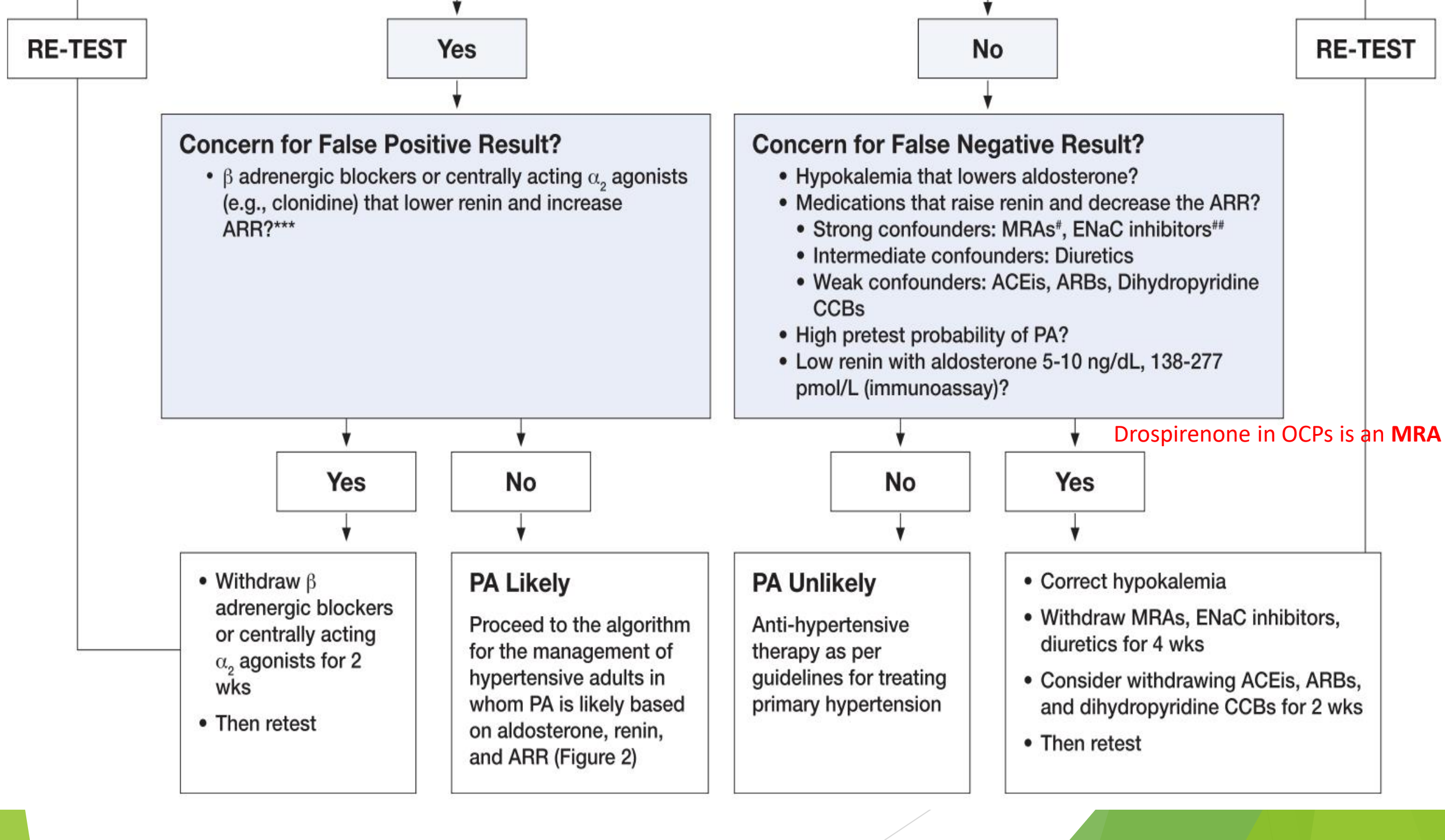
- ***Elderly patients*** with hypertension and patients with ***concomitant renal failure*** are more likely to have a low renin and increased ARR.

Screening of PA

- PA screening includes measurement of serum/plasma aldosterone concentration and plasma renin (concentration or activity) with determination of the aldosterone to renin ratio (ARR).

- Potassium is also assessed—not for screening itself—but to aid in the accurate interpretation of aldosterone
  (refer to Question 3).


Individuals with Hypertension
Measure Aldosterone, Renin, and Potassium*
Meets Criteria for Primary Aldosteronism**
Renin concentration or activity is low or suppressed, while aldosterone concentration is inappropriately high relative to renin
• Plasma renin activity (PRA) ≤ 1 ng/mL/h
• Direct renin concentration (DRC) ≤ 8.2 mU/L
• Aldosterone (immunoassay) ≥ 10 ng/dL (≥ 277 pmol/L)
• Aldosterone (LC-MS/MS) ≥ 7.5 ng/dL (≥ 208 pmol/L)
AND
Aldosterone to renin ratio (ARR) is increased
• Aldosterone (immunoassay, ng/dL) / PRA (ng/mL/h) > 20
• Aldosterone (immunoassay, pmol/L) / DRC (mU/L) > 70
• Aldosterone (LC-MS/MS, ng/dL) / PRA (ng/mL/h) > 15
• Aldosterone (LC-MS/MS, pmol/L) / DRC (mU/L) > 52
RE-TEST
Yes
No
RE-TEST



Drospirenone in OCPs is an **MRA**

Table 5. PA screening: ARR cut points according to aldosterone and renin assay and unit measurements

Renin		Aldosterone concentration measured by immunoassay		Aldosterone concentration measured by LC-MS/MS	
		≥10 ng/dL	≥277 pmol/L	≥7.5 ng/dL	≥208 pmol/L
Plasma renin activity	**≤1 ng/mL/h**	>20	>555	>15	>416
	≤12.9 pmol/L/min	>1.55	>43	>1.16	>32
	≤0.28 ng/L/s	>71	>2000	>53	>1500
DRC	**≤5.2 ng/L**	>4.0	>111	>2.8	>82
	≤8.2 mU/L	>2.5	>70	>1.8	>52

The aldosterone, renin, and aldosterone to renin ratio (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 primary aldosteronism (PA), along with potential interfering medications and conditions. The AAR values are not bolded.

Abbreviations: DRC, direct renin concentration; LC-MS/MS, liquid chromatography–tandem mass spectrometry.

Table 7. Medications that interfere with PA screening and their effects on aldosterone and renin

Effect on renin or aldosterone	Medication
Lower renin	β-adrenergic blockers, central acting α_2-agonists (clonidine, α-methyldopa), NSAIDs Combined estrogen and progesterone-containing OCPs and HRT decrease DRC (impact on PRA described below)
Raise renin	MRAs, diuretics including ENaC inhibitors (amiloride, triamterene), ARBs, ACE inhibitors, SGLT2 inhibitors Combined estrogen and progesterone-containing OCPs and HRT increase PRA (impact on DRC described above) Drospirenone blocks the MR and thus increases PRA and DRC
Lower aldosterone	ARBs, ACE inhibitors, β-adrenergic blockers, central α_2-agonist (clonidine, α-methyldopa)
Raise aldosterone	Diuretics[a], MRAs Combined estrogen and progesterone-containing OCPs and HRT Drospirenone

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II–receptor blocker; CCB, calcium-channel blocker; DRC, direct renin concentration; HRT, hormone-replacement therapy; MRA, mineralocorticoid antagonist; NSAID, nonsteroidal anti-inflammatory drug; OCP, oral contraceptive; PRA, plasma renin activity; SGLT2, sodium-glucose cotransporter 2; ENaC, epithelial sodium channel.

[a]By promoting natriuresis, diuretics (including MRAs) may induce a rise in aldosterone secondary to a rise in renin/angiotensin II. In the case of thiazide or loop diuretics, however, this may be mitigated by the development of hypokalemia (which inhibits aldosterone production).

Table 6. Managing interfering antihypertensive medications during PA screening and interpretation of aldosterone, renin, and ARR

Management strategy	Medication to withdraw	Timeline of withdrawal	Replacement antihypertensive agents	Interpretation of negative screen	Interpretation of positive screen
No medication withdrawal	None	–	–	Possible false negative if moderate to high pretest probability Repeat screen on different day with minimal- or full-medication withdrawal strategy	Possible false positive if individual taking β-adrenergic blockers or centrally acting α_2-agonists (clonidine, α-methyldopa) Repeat screen after withdrawing these medications
Minimal medication withdrawal	Stop MRAs and ENaC inhibitors (amiloride, triamterene) Stop β-adrenergic blockers and centrally acting α_2-agonists (clonidine, α-methyldopa)	4 weeks before testing 2 weeks before testing	Hydralazine[a] α_1-adrenergic blockers Non-dihydropyridine CCBs Moxonidine	Possible false negative if moderate to high pretest probability Repeat screen on different day with full withdrawal strategy If pretest probability is low, then likely true negative	Likely true positive Proceed to algorithm (Fig. 2)

Table 6. Managing interfering antihypertensive medications during PA screening and interpretation of aldosterone, renin, and ARR

Management strategy	Medication to withdraw	Timeline of withdrawal	Replacement antihypertensive agents	Interpretation of negative screen	Interpretation of positive screen
Ideal full medication withdrawal	Stop MRAs, ENaC inhibitors (amiloride, triamterene), and other diuretics β-adrenergic blockers ACE inhibitors ARBs Dihydropyridine CCBs Centrally acting α_2-agonists (clonidine, α-methyldopa) SGLT2 inhibitors	4 weeks before testing 2 weeks before testing	Hydralazine[a] α_1-adrenergic blockers Non-dihydropyridine CCBs Moxonidine	Possible false negative if moderate to high pretest probability Repeat screen on different day. If repeat is negative, then likely true negative If pretest probability is low, then likely true negative	Likely true positive Proceed to algorithm (Fig. 2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II–receptor blocker; CCB, calcium-channel blocker; ENaC, epithelial sodium-channel, MRA, mineralocorticoid antagonist; SGLT2, sodium-glucose cotransporter 2.
[a]Ideally individuals receiving hydralazine should also be administered a negative chronotropic agent such as verapamil slow release to avoid reflex tachycardia.

- Screening tests should be performed by primary care clinicians or by specialists in an outpatient setting.

- Referral to specialized centers should be considered for aldosterone suppression testing, and, if positive, further subtyping to differentiate lateralizing from bilateral forms of PA.

Question 2. Should primary aldosteronism–specific therapy (medical or surgical) vs nonspecific antihypertensive therapy be used in individuals with primary aldosteronism?

Recommendation 2

In individuals with hypertension and primary aldosteronism (PA), we suggest PA-specific therapy (medical or surgical) (2 | ⨁⨁OO).

Technical remarks:

- In individuals with lateralizing PA who are not surgical candidates or do not desire surgery and in individuals with bilateral PA, medical treatment with mineralocorticoid receptor antagonists (MRAs) should be considered preferable over nonspecific antihypertensive therapy.

- ❑ In individuals with lateralizing PA who are surgical candidates and desire surgery, unilateral adrenalectomy should be considered preferable over nonspecific anti - hypertensive therapy.

PA – Specific therapy

- PA-specific treatment is associated with significant BP reduction (7, 86), which, in turn, is expected to result in a reduced rate of cerebrovascular, cardiovascular, and renal events.
- Furthermore, individuals with PA display lower rates of adverse events after diagnosis and initiation of PA-specific treatment than before diagnosis when the treatment is with general antihypertensive drugs (87, 88).

PA – Specific therapy

- Furthermore, therapies (medical or surgical) that directly target the increased aldosterone in PA reduce the excess cardiovascular, cerebrovascular, and renal complications associated with PA.

Question 3. Should aldosterone (serum/plasma, or urine), renin (concentration or activity), and the aldosterone to renin ratio vs hypokalemia (unprovoked or diuretic-induced) be used for screening for primary aldosteronism in individuals with hypertension?

Recommendation 3

In individuals with hypertension, we suggest primary aldosteronism (PA) screening with serum/plasma aldosterone concentration and plasma renin (concentration or activity) (2 | ⊕⊕OO).

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 the accurate interpretation of aldosterone—as low potassium may lead to a falsely low aldosterone.

Hypokalemia

- As hypokalemia is present in only a minority of PA individuals (9%-37%), and many individuals with PA have normal potassium levels (90).

- Aldosterone and renin testing can identify normokalemic individuals with PA, expanding detection to a broader hypertensive population.

- 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 .

A positive screen meets both of the following conditions in most circumstances:

1. Renin is low/suppressed (hallmark of diagnosis) and aldosterone is inappropriately high relative to renin: indicative of PA if plasma renin activity (PRA) is ≤1 ng/mL/h or direct renin concentration (DRC) is ≤8.2 mU/L AND serum/plasma aldosterone concentration is ≥10 ng/dL (≥277 pmol/L) when measured by immunoassay or ≥7.5 ng/dL (≥208 pmol/L) when measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS)

Technical remarks:

- 2. Elevated aldosterone to renin ratio (ARR): indicative of PA if the aldosterone [ng/dL] to PRA [ng/ mL/h] ratio is >20 or aldosterone [pmol/L] to DRC [mU/L] ratio is >70 when aldosterone is measured by immunoassay; the ARR indicative of PA is about 25% lower when aldosterone is measured by LC-MS/MS). (Fig. 1 and Table 5 for ARR cut points for differing assays and units).

- However, as with many diagnostic tests based on continuous variables, the sensitivity and specificity depend ***on the selected threshold***.

Technical remarks:

- 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.

Technical remarks:

- 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.

Technical remarks:

- 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.

Technical remarks:
(False - negative)

- If the individual's initial screen is negative and the pretest probability of PA is moderate to high (eg, hypokalemia and/or resistant hypertension) or renin is suppressed with aldosterone of 5 to 10 ng/ dL (138 to 277 pmol/L) by immunoassay, the test should be repeated on a different day.

False - Positive

- If the individual's initial screen is positive, but they are receiving medications (eg, β-adrenergic blockers and centrally acting α_2-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

False - Positive

- 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 .

New – Onset PA

or

False - Negative

- If all initial screening is negative, consider rescreening 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

- The ARR was effective at screening for PA, and most cases were ultimately diagnosed with bilateral PA.

- The presence of hypokalemia is associated with more severe forms of PA and is more common in the lateralizing subtype.

Question 4. Should care guided by aldosterone suppression testing vs no aldosterone suppression testing be used in individuals with positive primary aldosteronism screen before initiating primary aldosteronism–specific therapy (medical or surgical)?

Recommendation 4

In individuals who screen positive for primary aldosteronism (PA), we suggest 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 (2 | ⨁OOO).

Technical remarks:

Situations in which aldosterone suppression testing may be helpful include:

- In individuals with an intermediate probability of having lateralizing PA who are willing and able to undergo surgical adrenalectomy (Fig. 2).

Situations in which aldosterone suppression testing is *not* required prior to initiating PA-specific therapy include (Fig. 2) :

1 - In individuals with resistant hypertension or hypertension with hypokalemia and overt biochemical evidence of renin-independent aldosterone production (plasma renin activity [PRA] <0.2 ng/mL/h or direct renin concentration [DRC] <2 mU/L and plasma aldosterone concentration >15 ng/dL [>416 pmol/L] via liquid chromatography–tandem mass spectrometry [LC-MS/MS] assay or >20 ng/dL [>554 pmol/L] via immunoassay), aldosterone suppression testing is not recommended due to the risk of false-negative results, which may exceed the risk of false-positive screening results.

Situations in which aldosterone suppression testing is *not* required prior to initiating PA-specific therapy include : (cont)

2 – Individuals unwilling or unable to pursue adrenal venous sampling and adrenalectomy can be empirically treated with mineralocorticoid receptor antagonists (MRAs) based on screening results, without aldosterone suppression testing.

- Aldosterone suppression testing may still provide value in some cases for further documenting the diagnosis.

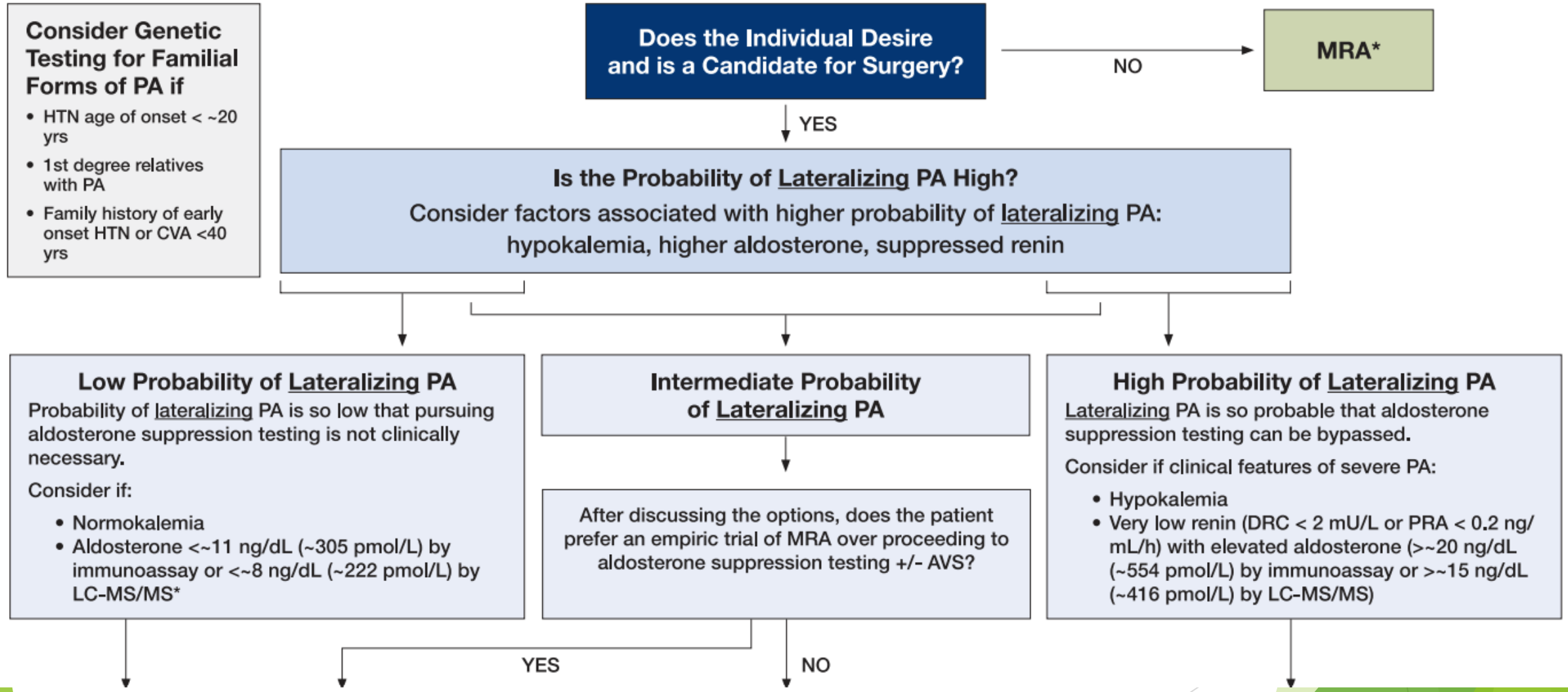
Situations in which aldosterone suppression testing is *not* required prior to initiating PA-specific therapy include : (cont)

3 - Aldosterone suppression testing is unnecessary in individuals from families with germline mutations associated with familial hyperaldosteronism.

- Genetic screening is recommended for all first degree relatives of individuals with familial hyperaldosteronism and for individuals with young - onset PA (<20 years) to enable early diagnosis and treatment.

Situations in which aldosterone suppression testing is *not* required prior to initiating PA-specific therapy include : (cont)

4 - Aldosterone suppression testing can also be avoided if the likelihood of lateralizing PA is so low that pursuing a formal diagnosis of PA is not justifiable (eg, normokalemia + plasma/serum aldosterone <~11ng/dL [<~305 pmol/L] [immunoassay] or <~8 ng/dL [<~222 pmol/L] [LC-MS/MS]).


Consider Genetic Testing for Familial Forms of PA if
• HTN age of onset < ~20 yrs
• 1st degree relatives with PA
• Family history of early onset HTN or CVA <40 yrs
Does the Individual Desire and is a Candidate for Surgery?
NO
MRA*
YES
Is the Probability of Lateralizing PA High?
Consider factors associated with higher probability of lateralizing PA: hypokalemia, higher aldosterone, suppressed renin
Low Probability of Lateralizing PA
Probability of lateralizing PA is so low that pursuing aldosterone suppression testing is not clinically necessary.
Consider if:
• Normokalemia
• Aldosterone <~11 ng/dL (~305 pmol/L) by immunoassay or <~8 ng/dL (~222 pmol/L) by LC-MS/MS*
Intermediate Probability of Lateralizing PA
After discussing the options, does the patient prefer an empiric trial of MRA over proceeding to aldosterone suppression testing +/- AVS?
YES
NO
High Probability of Lateralizing PA
Lateralizing PA is so probable that aldosterone suppression testing can be bypassed.
Consider if clinical features of severe PA:
• Hypokalemia
• Very low renin (DRC < 2 mU/L or PRA < 0.2 ng/mL/h) with elevated aldosterone (>~20 ng/dL (~554 pmol/L) by immunoassay or >~15 ng/dL (~416 pmol/L) by LC-MS/MS)

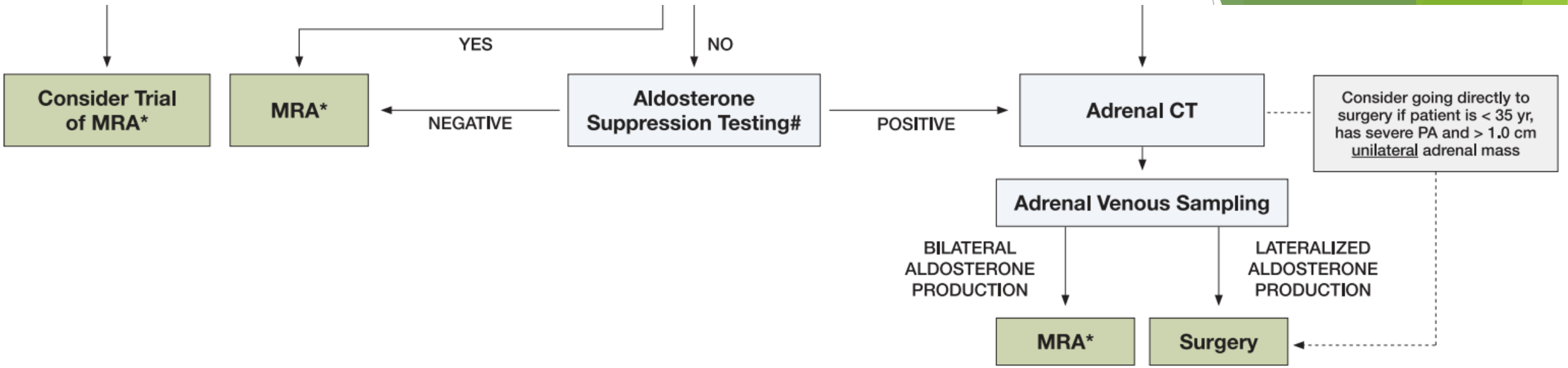


Figure 2. Algorithm for the management of adults with hypertension in whom PA is likely based on aldosterone, renin, and ARR. Patients who are likely to have PA, but have no desire for surgical adrenalectomy, or have contraindications to undergoing surgery, can be offered MRA therapy without further testing. MRA therapy is highly effective in PA. In addition, in studies of hypertensive individuals, MRAs have been consistently shown to be superior to alternative medication classes at lowering BP when renin is low or when the ARR is high (19-22). For patients who are interested in the possibility of, and capable of undergoing, unilateral adrenalectomy, probabilistic and shared decision making should be pursued. When the probability of lateralizing PA is low, patients can be offered MRA therapy without further testing. When the probability of lateralizing PA is high, cross-sectional adrenal imaging with CT and AVS can be pursued to adjudicate the possibility of lateralizing PA. When the probability of lateralizing PA is intermediate, or uncertain, shared decision making is advised. When possible, aldosterone suppression testing may be considered to steer the direction of management in individuals willing and able to undergo testing. In interpreting the aldosterone suppression test one should consider the possibility of false negatives (23-27). When aldosterone suppression testing is not available or desired, MRA therapy can be initiated. Approximate values for aldosterone and renin are provided for guidance. *See Fig. 3. Initiating and Following MRA Therapy. #False negatives may occur, may be impacted by local study conditions, and should be considered when deciding on whether to proceed to AVS testing.

aldosterone suppression testing:

- Some studies suggest that the results of aldosterone suppression testing predict the general likelihood that an individual may have lateralizing PA (ie, greater inability to suppress aldosterone indicates greater likelihood of lateralizing PA) (25, 100), thus providing clinicians with probabilistic information on when to refer for AVS or when to forego AVS in favor of targeted medical therapy.

Table 8. Description of the most commonly used aldosterone suppression tests

Aldosterone suppression test	Resource requirements	Protocol	Metrics	Interpretations	Comments
Oral sodium suppression test	Low	Individuals are instructed to consume 4-5 g of sodium per day for 3-4 days Collect 24-h urine collection on final day of high sodium intake	Measure urinary aldosterone, sodium, creatinine	24-h urine sodium should ideally be >200 mEq/ 24 hours 24-h urine creatinine is used to assess adequacy of urine collection 24-h urine aldosterone <10 mcg/nmol/24 hours makes PA unlikely (84)	Oral sodium can be consumed via sodium chloride tablets or sodium rich foods Because hypokalemia may cause false-negative interpretations, serum potassium should be normalized before the study protocol Interpretation of results is probabilistic and lacks evidence to recommend a precise diagnostic threshold (23) Protocol can be conducted in the ambulatory setting

Table 8. Description of the most commonly used aldosterone suppression tests

Aldosterone suppression test	Resource requirements	Protocol	Metrics	Interpretations	Comments
Captopril challenge test	Moderate	After sitting for 1 hour, blood is drawn to mark t = 0 Individuals are then given 50 mg of captopril and remain seated for 2 hours following administration Blood should be drawn at t = 2 hours to complete the study	Measure plasma aldosterone and renin at t = 0 and t = 2h	In the context of a post-captopril suppressed renin (<1.0 ng/mL/h or <10 mU/L), a 2-h post-captopril plasma aldosterone level <277 pmol/L (10 ng/dL) by immunoassay or <203 pmol/L (7.5 ng/dL) by LC-MS/MS makes PA unlikely (84) (112)	Many individuals with hypertension are actively treated with ACE inhibitors or ARBs; plasma aldosterone and renin values measured after taking these routinely prescribed medications may serve as a proxy for the captopril challenge test Interpretation of results should be considered to be probabilistic as the evidence to support a singular diagnostic threshold is not firm (26) Protocol requires an in-person visit and space and staff to accommodate the procedures

Table 8. Description of the most commonly used aldosterone suppression tests

Aldosterone suppression test	Resource requirements	Protocol	Metrics	Interpretations	Comments
Saline suppression test	Moderate	After sitting for 1 hour, blood should be drawn to mark t = 0 Two liters of normal saline are infused over 4 hours (500 mL/h for 4 hours), while maintaining a seated position, after which blood should be drawn	Measure plasma aldosterone and serum potassium at t = 0 and t = 4 hours	Plasma aldosterone <162 pmol/L (5.8 ng/dL) via LC-MS/MS assay makes PA unlikely Plasma aldosterone <217 pmol/L (7.8 ng/dL) via immunoassay assay makes PA unlikely (84, 100, 102, 113)	Because hypokalemia may cause false-negative interpretations, serum potassium should be normalized before the study protocol Interpretation of results should be considered to be probabilistic as the evidence to support a singular diagnostic threshold is not firm (25) Protocol requires an in-person visit, space and staff to accommodate the procedures, and IV infusion of saline Protocol should not be performed if baseline BP is uncontrolled, or in patients at high risk for pulmonary edema (such as in heart failure or advanced chronic kidney disease)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II–receptor blocker; IV, intravenous.

Question 5. Should primary aldosteronism–specific medical therapy vs surgical therapy be used in individuals with diagnosed primary aldosteronism?

Recommendation 5

In individuals with primary aldosteronism (PA), we suggest medical therapy or surgical therapy with the choice of therapy based on lateralization of aldosterone hypersecretion and candidacy for surgery (2 | ⊕OOO).

- **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 . (Fig. 2)

- ***Lifelong medical therapy*** that includes a mineralocorticoid receptor antagonist (MRA) is usually offered to individuals with bilateral PA or lateralization status unknown (refer to Question 6 for definition of lateralization) and to those who are not surgical candidates or who decline the surgical option . (Fig. 2)

- **Technical remarks:**

- 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. (Fig. 2)

- Individuals with multiple comorbidities who may not be good surgical candidates may also proceed directly to medical therapy. (Fig. 2)

Medical vs surgical management :

- The systematic review (53) assessed the comparative efficacy of medical vs surgical management for cardiovascular risk.
- No statistically significant differences were found between the 2 treatment modalities for ischemic heart disease, atrial fibrillation, MACEs, and cardiovascular mortality.
- However, compared with surgical therapy, review of observational studies indicated medical management had ***an increased risk of stroke*** (OR: 1.821; 95% CI: 1.144-2.898).

Medical vs surgical management :

- Medical treatment is cheaper and requires fewer resources (124). However, in an individual with PA and a remaining life expectancy of 25.4 years or more, surgery was estimated as the least costly strategy in the long-term due to the decreased risk of PA-associated adverse events (125).

- Adherence may improve with the use of more selective MRAs, such as *eplerenone* and potentially *finerenone* (127-129).

- Adrenalectomy appeals to individuals seeking a definitive cure for hypertension.

Medical vs surgical management :

- Thus, surgical treatment is generally preferred by individuals with lateralizing PA and may offer superior outcomes, but the choice between surgical and medical management should be based on individual characteristics, preferences, and the specific presentation of the disease.

Question 6. Should care guided by adrenal lateralization with computed tomography scanning and adrenal venous sampling vs computed tomography scanning alone be used for deciding treatment approach in individuals with primary aldosteronism?

Recommendation 6

In individuals with primary aldosteronism (PA) considering *surgery*, we suggest adrenal lateralization with computed tomography (CT) scanning and adrenal venous sampling (AVS) prior to deciding the treatment approach (medical or surgical) (2 | ⨁⨁OO).

Technical remarks:

- Individuals with PA who desire and are candidates for adrenalectomy should undergo AVS in order to reliably differentiate lateralizing from bilateral forms.

- Except :

- 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).

Justification for the Recommendation

- CT (or MRI) cannot assess the functional activity of adrenal glands and may misclassify individuals, particularly those with *bilateral adrenal hyperplasia* or *nonfunctional adrenal nodules*.

- Thus, in individuals who are surgical candidates, an additional localization step is needed, and the most accurate currently available option is AVS.

- AVS success rates depend on the experience of the operators and thus performance in centers with high expertise is recommended (143).

AVS

Three protocols have been used successfully for AVS:

1. Unstimulated sequential or simultaneous bilateral AVS;

2. Unstimulated sequential or simultaneous bilateral AVS followed by bolus cosyntropin-stimulated sequential or simultaneous bilateral AVS; and

3. Continuous cosyntropin infusion with sequential bilateral AVS.

Simultaneous bilateral AVS is difficult to perform and is not used at most centers (145,146).

Table 9. Key indices and cutoffs for adrenal vein sampling interpretation

AVS index	Index formula	Cutoff values	Diagnostic significance
Selectivity index (SI)	$[\text{cortisol}]_{AV}/[\text{cortisol}]_{IVC}$	Unstimulated >1.4 to 3 Cosyntropin-stimulated >5	Indication of successful AV cannulation
Lateralization index (LI)	$([\text{aldosterone}]/[\text{cortisol}])_{highAV}/([\text{aldosterone}]/[\text{cortisol}])_{lowAV}$	Unstimulated or cosyntropin-stimulated ≥4	Distinguishes lateralizing from bilateral PA
Contralateral suppression index (CSI)	$([\text{aldosterone}]/[\text{cortisol}])_{lowAV}/([\text{aldosterone}]/[\text{cortisol}])_{IVC}$	Unstimulated or cosyntropin-stimulated <1	Consistent with suppressed aldosterone production by the contralateral adrenal gland

Abbreviations: AV, adrenal vein; highAV, adrenal vein measurement from the dominant adrenal; IVC, inferior vena cava; lowAV, adrenal vein measurement from the nondominant adrenal gland.

AVS

- However, there is a lack of consensus on the use of cosyntropin stimulation to assess for lateralization (150)
- Aldosterone and cortisol concentrations are measured in the blood from all 3 sites (right and left adrenal veins and inferior vena cava [IVC]).
- The IVC sample may be obtained from veins that are even more peripheral (eg, external iliac vein) (141).

- All of the blood samples should be assayed at 1:1, 1:10, and 1:50 dilutions; absolute values and accurate laboratory assays for cortisol and aldosterone are essential for successful interpretation of the AVS data.

AVS

- For accurate interpretation of AVS, it is important that serum potassium concentration is normal and renin is suppressed.
- It is also important that blood pressure is well controlled, and this may necessitate the use of antihypertensive agents.

Question 7. Should suppressed renin vs unsuppressed renin be used in individuals with primary aldosteronism receiving primary aldosteronism–specific medical therapy?

Recommendation 7

- In individuals with primary aldosteronism (PA) receiving PA-specific medical therapy whose hypertension is not controlled and renin is suppressed, we suggest increasing PA-specific medical therapy to raise renin (2 | ⨁OOO)

Renin

- 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.

- Our systematic review (53) identified 11 studies that evaluated the impact of increasing renin with aldosterone-directed medical therapy when compared with persistently suppressed renin.
- When compared with unsuppressed renin, suppressed renin during aldosterone-directed medical therapy was associated with *increases in mortality*; risk for *stroke*, *atrial fibrillation*, and *hypokalemia*; and *number of antihypertensive medications.*

Renin

- However, achieving a rise in renin is suggested as an additional objective that reflects a better prognosis (175).
- we suggest focusing on dose intensification of MRA therapy to raise renin, particularly in individuals whose BP is not controlled.
- A recent large international consensus group endorsed targeting a rise in renin when implementing aldosterone-directed medical therapy to a level higher than 1.0 ng/mL/h (plasma renin activity [PRA]) or 10 mU/L (direct renin concentration [DRC]) (85).

PA & CKD

- It is reasonable to treat individuals with PA and CKD with MRAs as long as serum potassium is monitored.

- When encountering hyperkalemia in CKD, the use of concurrent diuretics, sodium-glucose cotransporter (SGLT2) inhibitors, and ***patiromer***/novel potassium binders have all been shown to mitigate the risk of MRA-induced hyperkalemia in RCTs (179, 180).

Question 8. Should a dexamethasone suppression test vs no dexamethasone suppression test be used in individuals with primary aldosteronism and adrenal adenoma?

Recommendation 8

- In individuals with primary aldosteronism (PA) and adrenal adenoma, we suggest a dexamethasone suppression test (2 | ⨁OOO).

Technical remarks

- 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 ACS, measuring plasma *metanephrine* during adrenal venous sampling (AVS) may help lateralize both aldosterone and cortisol secretion although further research is needed.

PA + ACS

- ***5% to 15%*** of individuals with PA have ACS .
- A more recent systematic review of 16 studies published between 2000 and 2020, with data from 2862 individuals with PA, reported a prevalence of ***5% to 27%*** (187) .
- The adverse consequences include : *worse glucose tolerance* and *diabetes* (188-191), *higher left ventricular mass index* (192), more *cardiovascular events* (189, 193), *osteopenia/osteoporosis* (189, 194), and *renal dysfunction* (195).

PA + ACS

- It will also be important to measure early morning cortisol following adrenal surgery and prepare for a period of possible *glucocorticoid insufficiency*.
- Repeating AVS due to uninterpretable results is much more expensive (~$2000-3000 USD)

Question 9. Should spironolactone vs other mineralocorticoid receptor antagonists be used for primary aldosteronism–specific medical therapy?

Recommendation 9

- In individuals with primary aldosteronism (PA) receiving PA-specific medical therapy, we suggest ***spironolactone*** over other mineralocorticoid receptor antagonists (MRAs) due to its low cost and widespread availability (2 | ⨁OOO).

Technical remarks:

- MRAs with greater mineralocorticoid receptor (MR) specificity and fewer androgen/progesterone receptor-mediated side effects may be preferred.

- Monitor potassium, renal function, renin (concentration or activity), and blood pressure (BP) response during follow-up to guide MRA dose titration.

Comparing of MRAs

- A new study comparing short-term ***finerenone*** and low-dose ***spironolactone*** in PA was published demonstrating comparable blood pressure–lowering efficacy and effects upon serum potassium and renin concentration (213).

- MRA drugs such as : ***esaxerenone***

- Aldosterone synthase inhibitors : ***dexfadrostat***

Question 10. Should epithelial sodium-channel inhibitors vs mineralocorticoid receptor antagonists (steroidal and nonsteroidal) be used for medical treatment of primary aldosteronism?

Recommendation 10

- For individuals with primary aldosteronism (PA) receiving PA-specific medical therapy, we suggest using mineralocorticoid receptor antagonists (MRAs) rather than epithelial sodium-channel (ENaC) inhibitors (amiloride, triamterene) (2 | ⨁OOO).

Technical remark:

- The recommendation (see Fig. 3) does not apply to clinical conditions in which spironolactone is contraindicated (eg, *hyperkalemia*, *advanced renal impairment*, or *pregnancy*) or if a non-spironolactone MRA were indicated for other non-PA indications (eg, *heart failure*).

Comparing MRAs with ENaC Inh.

- The largest study was a sub-study of the ***PATHWAY-2*** study, which was a randomized, double-blind crossover trial in individuals with resistant hypertension (19). Results showed similar BP-lowering effects of spironolactone and amiloride.

- In the spironolactone, amiloride, losartan, and thiazide ***(SALT)*** double-blind crossover trial in individuals with low-renin hypertension and elevated aldosterone to renin ratio (ARR), spironolactone and high-dose amiloride had similar antihypertensive effects (226).

Amiloride

- Amiloride may be an effective antihypertensive drug in individuals with PA .
- Amiloride at higher doses corrected hypokalemia and normalized BP in individuals with PA (228).

Comparing MRAs with ENaC Inh.

- A major assumption (as required with reliance on indirect evidence) is that both ENaC inhibitors and MRAs would likely yield equivalent clinical outcomes based on observations that they probably yield similar BP reductions in a PA population.

- However, ENaC inhibitors do not block aldosterone directly; therefore, the impact of ENaC inhibitors and MRAs on aldosterone-specific end-organ injury may differ.

Table 10. Comparisons of MRA and ENaC inhibitors[a]

Drug	Typical starting dose in PA	Possible maximum dose in PA[b]	Usual cost
Spironolactone	12.5-25 mg/d	200 mg/d	$
Eplerenone	25-50 mg twice daily	200 mg twice daily	$$-$$$
Finerenone[c]	Unknown; 10-20 mg/d	unknown	$$$$
Amiloride	5-10 mg/d	40 mg/d	$
Triamterene[d]	50-100 mg/d	300 mg/d	$

[a]Data are very limited, mostly from observational studies using fixed doses in hypertension, uncertain outcomes and titration protocols.
[b]Specialist consultation recommended if doses above these ranges appear to be necessary.
[c]Data are very limited in PA individuals.
[d]Often supplied as combination with hydrochlorothiazide.

سپاس از توجه و حضور شماگرامیان