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Clinical Practice Guideline

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

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Abstract

Background: Primary aldosteronism (PA), a primary adrenal disorder leading to excessive aldosterone production by one or both adrenal glands, is a common cause of hypertension. It is associated with an increased risk of cardiovascular complications compared with primary hypertension. Despite effective methods for diagnosing and treating PA, it remains markedly underdiagnosed and undertreated.

Objective: To develop an updated guideline that provides a practical, clinical approach to identifying and managing PA to improve diagnosis rates and encourage targeted treatment.

Methods: The Guideline Development Panel (GDP), composed of a multidisciplinary panel of clinical experts and experts in systemic review methodology, used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to define 10 questions related to the diagnosis and treatment of PA. Systematic reviews were conducted for each question. The GDP used the GRADE Evidence to Decision (EtD) framework to consider contextual factors, such as stakeholder values and preferences, costs and required resources, cost-effectiveness, acceptability, feasibility, and the potential impact on health equity.

Results: We suggest that all individuals with hypertension be screened for PA by measuring aldosterone and renin and determining the aldosterone to renin ratio, and that subsequent clinical care be guided by the results. We suggest that individuals with PA receive PA-specific therapy, either medical or surgical. In individuals who screen positive for PA, we suggest (1) commencement of PA-specific medical therapy in individuals who do not desire or are not candidates for surgery and in situations where the probability of lateralizing PA (excess aldosterone produced by one adrenal) is low based on screening results; and (2) aldosterone suppression testing in situations when screening results indicate an intermediate probability for lateralizing PA and individualized decision making confirms a desire to pursue eligibility for surgical therapy. In those who test positive by aldosterone suppression testing, and in those in whom screening results show a high probability of lateralizing PA (obviating the need for aldosterone suppression testing), we suggest adrenal lateralization with computed tomography scanning and adrenal venous sampling prior to deciding the treatment approach (medical vs surgical). In all individuals with PA and an adrenal adenoma, we suggest performing a 1-mg overnight dexamethasone suppression test. We suggest the use of mineralocorticoid receptor antagonists (MRAs) over epithelial sodium-channel (ENaC) inhibitors in the medical treatment of PA. We suggest the use of spironolactone over other MRAs, given its lower cost and greater availability; however, all MRAs, when titrated to equivalent potencies, are anticipated to have similar efficacy in treating PA. Thus, MRAs with greater mineralocorticoid receptor specificity and fewer androgen/progesterone receptor-mediated side effects may be preferred in some situations. In individuals receiving MRA therapy, we suggest monitoring renin and, in those whose hypertension remains uncontrolled and renin is suppressed, titrating the MRA to increase renin.

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Conclusion: These recommendations provide a practical framework for the diagnosis and treatment of PA. They are based on currently available literature and take into consideration outcomes that are important to key stakeholders. The goal is to increase identification of individuals with PA and, by initiating PA-specific medical or surgical therapy, improve blood pressure control and reduce PA-associated adverse cardiovascular events. The guidelines also highlight important knowledge gaps in PA diagnosis and management.

Key Words: Primary aldosteronism, secondary hypertension, clinical practice guideline, aldosterone

Abbreviations: ACE, angiotensin-converting enzyme; ACS, autonomous cortisol secretion; APA, aldosterone-producing adenoma; ARB, angiotensin receptor blocker; ARR, aldosterone to renin ratio; AVS, adrenal venous sampling; BP, blood pressure; CKD, chronic kidney disease; CT, computed tomography; DRC, direct renin concentration; ENaC, epithelial sodium-channel; EtD, Evidence to Decision; GDP, Guideline Development Panel; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IVC, inferior vena cava; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MACE, major adverse cardiovascular event; MD, mean difference; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; MRI, magnetic resonance imaging; OR, odds ratio; PA, primary aldosteronism; PET, positron emission tomography; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial; QOL, quality of life; SBP, systolic blood pressure.

Primary aldosteronism (PA) is an adrenal disorder, either unilateral or bilateral, resulting in excess adrenal production of aldosterone. In PA, aldosterone production is at least partially autonomous of its normal major regulator, the renin–angiotensin system, circulating levels of which are suppressed. The excess aldosterone leads to renal sodium retention, volume expansion, elevated blood pressure (BP), and, in more severe forms, hypokalemia.

Compared with those with primary hypertension, individuals with PA face significantly higher health risks (1,2). 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). 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). Despite its prevalence and the serious health risks it poses, PA remains largely underdiagnosed and undertreated. This under-recognition contributes significantly to the health care costs associated with hypertension, including the management of complications and related productivity losses.

Screening for PA is critically low, often delayed until years after hypertension has been diagnosed, typically following the emergence of severe complications. This may in part be due to misconceptions that PA is only present in the setting of hypokalemia, adrenal macro-nodules, frankly elevated aldosterone levels, or severe hypertension. As a result, many individuals continue to be treated for primary hypertension, thus missing out on targeted treatments or potential cures, and enduring suboptimally managed BP and increased risks of cardiovascular and renal disease. The importance of this is emphasized in the latest major clinical guidelines on hypertension: 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). The morbidity and mortality associated with PA are largely preventable. Individuals with lateralizing PA can often be cured through unilateral adrenalectomy. Those with bilateral PA typically benefit from treatment with mineralocorticoid receptor antagonists (MRAs), such as spironolactone or eplerenone, which effectively control BP, alleviate hypokalemia, and mitigate excess cardiovascular risk associated with PA (7-9). Despite these advantages, MRAs are not routinely used as first-line treatments for hypertension, resulting in missed diagnostic and therapeutic opportunities for those with undiagnosed PA.

The Guideline Development Panel (GDP)'s primary objective for the updated guideline was to support the clinical approach to screening and managing PA, thereby replacing the previous guideline of the Endocrine Society. This revision underscores the urgent need to assist clinicians in navigating key clinical practice questions related to PA. Specifically, the panel asked 10 critical questions, starting with whether all individuals with hypertension should be screened for PA and whether PA-specific therapy leads to superior clinical outcomes as compared to nonspecific antihypertensive therapy. These first 2 questions demonstrate the critical need to diagnose and specifically treat PA by demonstrating that PA is a common cause of secondary hypertension, that it is associated with increased cardiovascular risk compared with primary hypertension, and that PA-specific therapy reduces these risks. Subsequent questions concern the selection of appropriate tests to screen for PA, the need for aldosterone suppression testing, dexamethasone suppression testing and adrenal venous sampling, and options for medical and surgical management.

To develop these recommendations, we employed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. A systematic review was conducted for each question, revealing a general scarcity of randomized clinical trials and leaving the panel to rely on observational studies. The panel sought evidence relevant to all elements of the GRADE Evidence to Decision (EtD) framework, including stakeholder values and preferences (drawing on input from clinical experts and a patient representative), costs and other resources required, cost-effectiveness, acceptability, feasibility, and potential impact on health equity. However, the panel did not identify robust evidence addressing these EtD considerations for most clinical questions

To enhance the practical application of these recommendations, the panel developed a series of tools aimed at increasing their usefulness. These tools include algorithms to guide clinicians through the screening and management of PA, detailed steps for the medical management of PA, and a decision aid for making informed choices about the use of MRAs for individuals with PA. Additionally, the panel included suggestions for future research studies in each recommendation. These suggestions aim to address existing gaps in evidence for critical clinical questions, thereby fostering a deeper understanding and improving the management of PA.

Methods of Development of Evidence-Based Clinical Practice Guidelines

This guideline was developed using the process detailed on the Endocrine Society website located here: https://www.

Table 1. GRADE certainty of evidence classifications

Certainty of evidence	Interpretation
High ⊕⊕⊕⊕	There is high confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a specific range.
Moderate ⊕⊕⊕O	There is moderately confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate slightly from the target of the certainty rating (i.e. may possibly fall in a different range).
Low ⊕⊕OO	There is low confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate from the target of the certainty rating (i.e. likely fall in a different range).
Very Low ⊕OOO	There is very-low confidence that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate significantly from target of the certainty rating (i.e. probably fall in a different range).

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GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Adapted with permission from Neumann I, Schünemann H (Editors). The GRADE Book version 1.0 (updated September 2024). The GRADE Working Group (12).

Table 2. GRADE strength of recommendation classifications and interpretation

Strength of recommendation	Criteria	Interpretation by individuals	Interpretation by health care clinicians	Interpretation by policy makers
1: Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa).	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2: Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa).	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Adapted from Schünemann HJ et al *Blood Adv,* 2018; 2(22):3198-3225. © The American Society of Hematology, published by Elsevier (13).

endocrine.org/clinical-practice-guidelines/methodology (10). The Endocrine Society follows the GRADE approach (11) (Tables 1 and 2), which includes EtD frameworks to ensure all important criteria are considered when making recommendations (14). The process was facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT) (15). The GDP consisted of content experts representing the following clinical specialties: endocrinology, general internal medicine, genetics, hypertension specialists, epidemiology, and a patient representative. Members were identified by the Endocrine Society Board of Directors and the Clinical Guidelines Committee and were vetted according to the Endocrine Society's conflict-of-interest policy, which was followed throughout the guideline process to manage and mitigate conflicts of interest. Detailed disclosures of panel members and the management strategies implemented during the development process can be found in Appendix A. In addition, the group included a clinical practice guideline methodologist from the Mayo Evidence-Based Practice Center, who led the team that conducted the systematic reviews, and a methodologist from the Endocrine Society, who advised on methodology and moderated the application of the EtD framework and development of the recommendations.

A group of 2 to 3 GDP members were assigned to lead each guideline question. The 10 clinical questions addressed in this guideline were prioritized from an extensive list of potential questions through a survey of the panel members and discussion. The Mayo Evidence-Based Practice Center conducted a systematic review for each question and, when available, produced GRADE evidence profiles that summarized the body of evidence for each question and the certainty of the evidence (Murad in press). The systematic searches for evidence were conducted in February 2022 and updated in October 2024. In parallel with the development of the evidence summaries, the GDP members searched and summarized research evidence related to each question (generally observational studies) and to other EtD criteria, such as individuals' values and preferences, cost and resources required, cost-effectiveness, feasibility, acceptability, and the potential impact on health equity. Research evidence summaries noted in the EtD frameworks were compiled using standardized terminology templates for clarity and consistency (16). During 2 in-person panel meetings and a series of video conferences, the GDP judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of each recommendation (16-18) (Tables 1 and 2).

The draft recommendations were posted publicly for external peer review and internally for Endocrine Society members, and the draft guideline manuscript was reviewed by the Society's Clinical Guidelines Committee, representatives of any co-sponsoring organizations, a representative of the Society's Board of Directors, and an Expert Reviewer. Revisions to the guideline were made based on submitted comments and approved by the Clinical Guidelines Committee, the Expert Reviewer, and the Board of Directors. Finally, the guideline

manuscript was reviewed before publication by the *Journal of Clinical Endocrinology and Metabolism's* publisher's reviewers.

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

List of Recommendations

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).

Technical remarks:

- 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.
- This recommendation emphasizes care that is informed and guided by screening, with a positive screening result serving as the critical first step in the care process for individuals with 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).

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 antihypertensive therapy.

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.
- 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.
- Manage interfering medications depending on individual safety and feasibility. The Guideline Development Panel outlined both minimal-withdrawal and no-withdrawal strategies of interfering medications before screening (Tables 6 and 7, Fig. 1).
- 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)
  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).
- 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

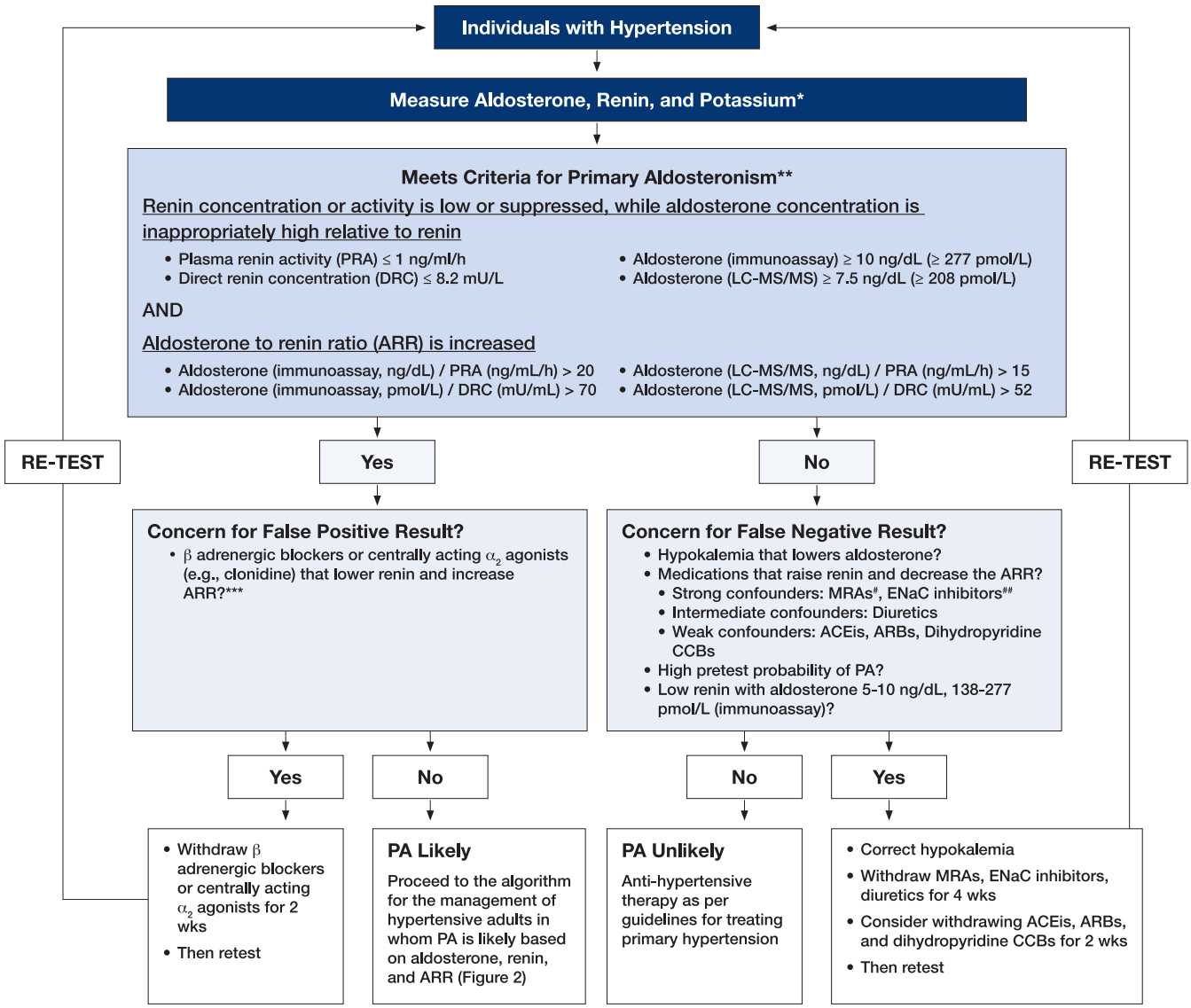


Figure 1. How to screen for PA in individuals with hypertension. This figure diagrams the process of screening for PA in individuals with hypertension. For individuals whose screening indicates likely PA, the next steps are diagrammed in Fig. 2, Algorithm for the Management of Adults with Hypertension in Whom PA is Likely Based on Aldosterone, Renin, and ARR. *Blood is obtained in seated position in the morning; ideally without venous stasis (release tourniquet after venipuncture and wait at least 5 seconds before withdrawing blood) to avoid factitious rises in potassium. **The aldosterone, renin, and ARR values provided in this figure and in greater detail in Table 5 are 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. ***Consider potential false positive induced by β-adrenergic blockers when aldosterone <15 ng/dL (< 415 pmol/L) by immunoassay, <10 ng/dL (< 277 pmol/L) by LC-MS/MS. #Drospirenone in OCPs is an MRA. ##Amiloride and triamterene are ENaC inhibitors.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II–receptor blocker; CCB, calcium-channel blocker; DRC, direct renin concentration; ENaC, epithelial sodium-channel; HRT, hormone-replacement therapy; LC-MS/MS: liquid chromatography–tandem mass spectrometry; MRA, mineralocorticoid antagonist; OCP, oral contraceptive; PRA, plasma renin activity; SGLT2, sodium-glucose cotransporter 2.

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 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.
- 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.
- 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 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

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):

- 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.
- 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.
- 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.
- 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]).

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).

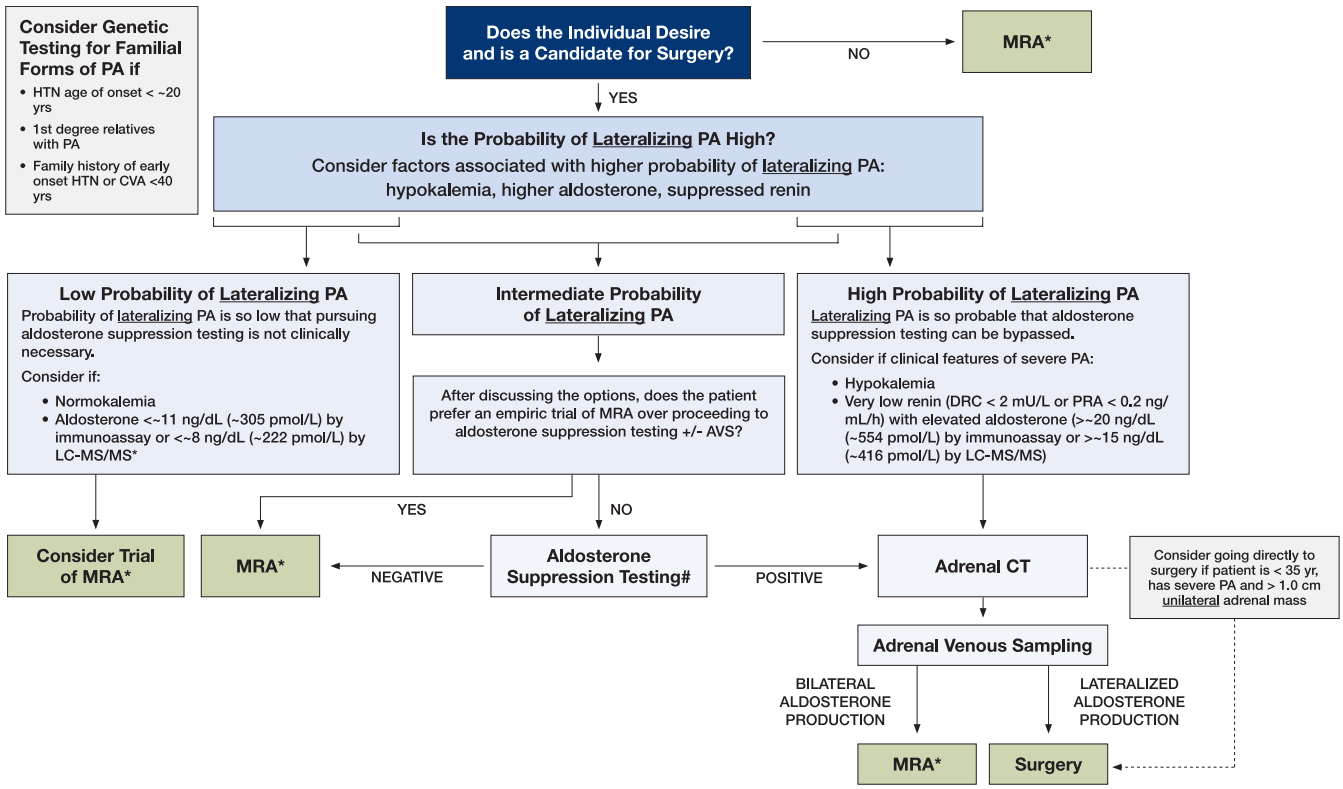


Figure 2. Algorithm for the management of adults with hypertension in whom PA is likely based on aldosterone, renin, and ARR. Patients who are likely to have PA, but have no desire for surgical adrenalectomy, or have contraindications to undergoing surgery, can be offered MRA therapy without further 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.

Abbreviations: HTN, hypertension; CVA, cerebrovascular accident; MRA, mineralocorticoid antagonist.

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).
- 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).

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.

- 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).

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).

Technical remarks:

- 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.

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:

- 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.

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:

- 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 (Fig. 3).
- Monitor potassium, renal function, renin (concentration or activity), and blood pressure response during follow-up to guide MRA dose titration.

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).

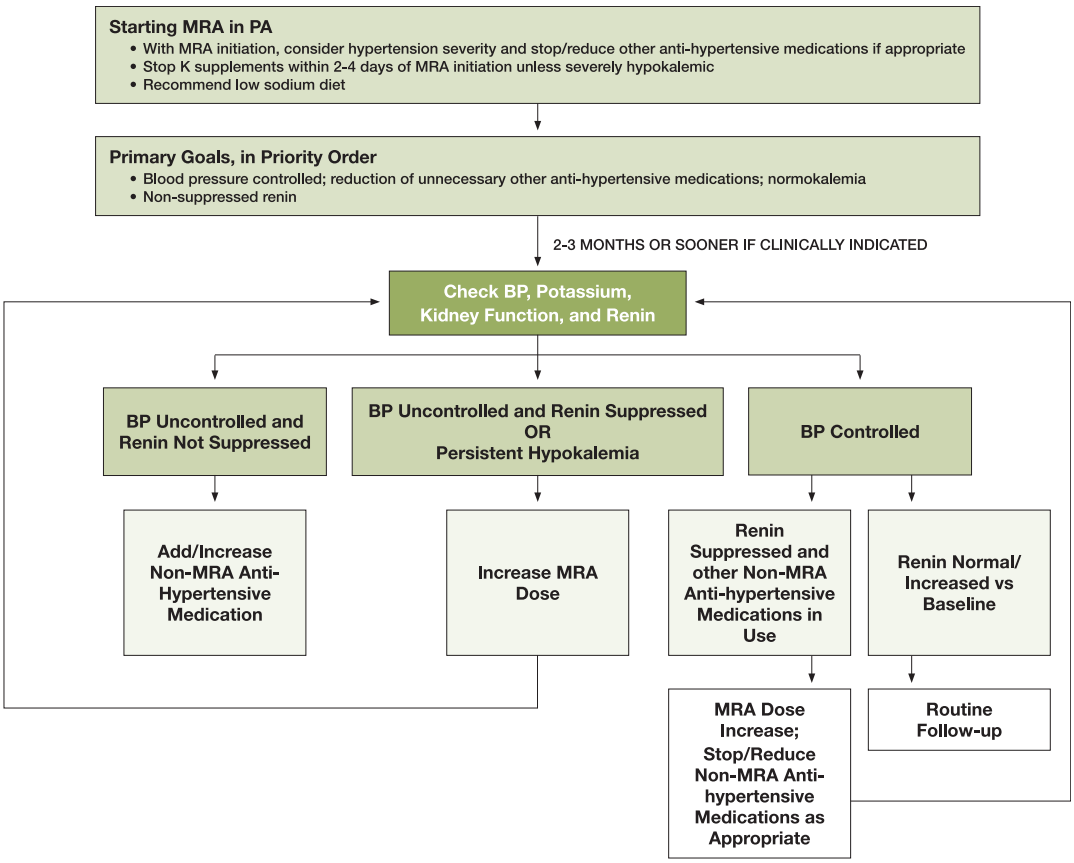


Figure 3. Initiating and following MRA therapy. This is a general guide and there is a wide range of inter-patient responsiveness to varying doses of MRA. The process of MRA initiation and titration is expected to be multi-step for many patients; each MRA adjustment is followed by an assessment of both BP and biochemical response, then re-entering the treatment algorithm as appropriate. The primary goal of therapy is control of BP. The secondary goal of therapy is achievement of normokalemia. Measurement of renin (as a marker of MR blockade) may assist in the process of MRA dose titration for achieving these goals and possibly reducing other non-MRA antihypertensive drugs.

1. 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).
2. 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 panelists 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) (6).
3. 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 (28). Typical doses required to de-suppress renin are variable and likely higher than doses used as empiric add-on for resistant hypertension (29) (30); 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 uptitrated. 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.
4. 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 (31); 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.
5. The glomerular filtration rate (GFR) may decrease in individuals with PA on introduction of PA-targeted medical therapy or with successive titration of MRA (32, 33). The time course of change may be over days to weeks and, in most cases, represents a marker of treatment efficacy as opposed to adverse effect. The natural history of an appropriate treatment-induced decrease in GFR is usually one of eventual long-term stability, anticipating a renal-sparing effect of effective MRA therapy (32, 33). If renal function progressively declines, consider referring to nephrology and discontinuing ACE inhibitors or ARBs.
6. 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 (see Question 10). This almost always allows complete resolution of the gynecomastia if it has not already progressed to advanced size.
7. 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.

Who Should be Screened for Primary Aldosteronism?

Background

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

PA is characterized by excessive production of aldosterone (49), leading to higher blood pressure (BP), renal injury, and an elevated risk of stroke, atrial fibrillation, and other cardiovascular diseases (1, 2). Detection of PA allows the use of specific treatments—such as mineralocorticoid receptor antagonists (MRAs), or adrenalectomy for those with lateralizing disease—that can effectively control BP, correct hypokalemia, and reduce cardiovascular risk (7-9)

Despite the potential benefits of treatment, PA remains underdiagnosed, in part due to limited screening in routine clinical practice (50, 51). Many individuals with PA, even those with high-risk features, such as resistant hypertension and hypokalemia (52), are never identified, leading to suboptimal management of their hypertension and cardiovascular risk. Expanding PA screening to all hypertensive individuals could increase the detection rate, allowing more individuals to benefit from targeted therapies and potentially reducing long-term cardiovascular risks.

However, the benefits of widespread screening must be weighed against certain challenges. The accuracy of screening tests, such as aldosterone concentration, renin concentration or activity, and the aldosterone to renin ratio (ARR), is influenced by various factors, including medication use, dietary sodium intake, and test conditions. False positives can occur, resulting in unnecessary aldosterone suppression testing or even inappropriate PA treatment in individuals without the condition. Access to diagnostic and subtyping tests and the availability of specialized treatments may also undermine the feasibility of universal screening unless alternative strategies are proposed.

Therefore, the guideline addresses the question of whether care with PA screening should be implemented for all individuals with hypertension.

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).

Technical remarks:

- 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.
- This recommendation emphasizes care that is informed and guided by screening, with a positive screening result serving as the critical first step in the care process for individuals with 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).

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at: https://guidelines.gradepro.org/profile/goKsLjFSyDQ.

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)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Grades 1, 2, and 3 hypertension refer to the classification of the 2023 European Society of Hypertension guideline (48). Grade 1, SBP 140-159 mmHg and/or DBP 90-99 mmHg; grade 2, 160-179 mmHg and/or DBP 100-109 mmHg; grade 3, SBP ≥180 mmHg and/or DBP ≥110 mmHg.
[b]If unexplained by structural heart disease and other conditions like hyperthyroidism.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 1 decision making: 1) percent of individuals achieving BP control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) major adverse cardiovascular events (MACEs), 6) atrial fibrillation, 7) stroke, 8) ischemic heart disease, 9) heart failure, 10) cardiovascular mortality, 11) all-cause mortality, and 12) adverse events.

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). Testing for PA was associated with a 4-fold higher likelihood of initiating treatment with an MRA. Individuals who underwent PA testing also had an average 1.47-mmHg lower SBP over time compared with those not tested. Certainty of evidence for the outcome of BP control is low due to the nonrandomized nature of the study and indirectness. The panel did not identify any head-to-head studies comparing screening vs no screening for the outcomes of interest.

Due to the limited availability of studies directly evaluating the comparative effectiveness and potential harms of screening, this recommendation relies on indirect evidence. The panel used a guideline screening framework that considers multiple factors required to justify screening (54). The panel also adopted a framework based on Wilson and Jungner's principles of screening (55). This framework, as relevant to screening for PA, is detailed in Table 4.

PA is recognized as an important health problem. It is common, affecting 5% to 14% of hypertensive individuals in the primary care population and up to 30% in referral centers (34, 38, 35, 36). Untreated PA confers a higher risk of cardiovascular complications, with a meta-analysis of 31 studies showing an increased risk of stroke, coronary artery disease, atrial fibrillation, and heart failure for individuals with PA compared with BP-matched primary hypertension (2).

While the natural history of PA is not fully understood, due to the general lack of screening from a young age, multiple studies provide evidence that elevated aldosterone concentration, especially in the presence of low renin concentration or activity, is associated with increased risk of hypertension and cardiovascular events over time. For example, data from the Framingham Heart Study demonstrate that individuals with aldosterone levels in the higher quartiles of the normal distribution are more prone to develop hypertension or to have an increase in BP during the follow-up period than individuals with lower aldosterone levels (56). Furthermore, higher aldosterone levels predict the development of chronic kidney disease and microalbuminuria (57). The effect of aldosterone on hypertension development is more evident in individuals with low renin (ie, those with a higher ARR) (58, 59), with the ratio being associated with incident hypertension in different population studies (58, 60, 61). Renin-independent aldosteronism (with low renin), in contrast to renin-dependent aldosteronism, is associated with higher cardiovascular risk (62). The ARR in healthy individuals also correlates with vascular stiffness (63). These data were replicated in a Canadian population (64), which showed that, independent of BP, a biochemical phenotype of subclinical PA is negatively associated with cardiovascular health, including greater arterial stiffness,

Table 4. Evidence for the recommendation of primary aldosteronism screening

Importance *The condition should be an important health problem.*	PA is a frequent cause of secondary hypertension. PA, independent of blood pressure, is associated with increased mortality and morbidity if untreated.
Natural History *The condition being screened for should have a natural history that is understood and a recognized latent period.*	Individuals with PA develop organ damage and cardiovascular events if left untreated.
Difference in Management *Individuals with a positive screening test would receive different care than those with a negative test.*	Individuals with a positive screening test are candidates for PA-targeted therapy.
Available Treatment *Effective treatment should be available for the condition that improves outcomes if administered earlier than when the condition is clinically apparent.*	Specific medical therapies are available and effective. Also, adrenalectomy for lateralizing subtypes of PA is effective. PA-specific therapies reduce the rate of cardiovascular complications. Novel therapies are under investigation.
Difference in Outcomes *Improvement in outcomes based on management according to screening results outweighs harms of screening.*	Individuals with PA display a significant benefit from targeted treatment, with the possibility of cure in those with surgically resectable lateralizing adrenal disease. Individuals with potentially false-positive results are not exposed to harm if treated with aldosterone-blocking drugs since they also proved effective in individuals with primary hypertension. Careful selection for individuals undergoing AVS should be made to avoid unnecessary invasive procedures. Harms associated with screening are minimal as we provide pathways for screening that involve no or minimal withdrawal of current antihypertensive medications.
Accuracy *Certainty of evidence for a sufficient accuracy of the test is high or moderate.*	Screening tests are sufficiently accurate. False-negative results may be observed in mild forms or may be caused by variability in aldosterone concentration; aldosterone suppression testing can help to confirm PA.
Other Considerations *Screening should be cost-effective, acceptable to individuals, and feasible to implement.*	Screening for PA is cost-effective, convenient, and accepted by the individuals. Feasibility depends on collaboration between general practitioners, specialists, laboratories, and referral centers.

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 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)
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.

adverse cardiac remodeling, and incident hypertension. In the ARIC study (65), low renin and high aldosterone levels are associated with cardiac structural and functional alterations. Even in adults as young as 27 years of age, aldosterone concentrations or the ARR have been found to correlate with left ventricular mass index (66).

Management is different if PA screening is incorporated, or not, into the care of individuals with hypertension. In the absence of specific recommendations for PA screening with measurement of aldosterone and renin in all individuals with hypertension, this blood test is rarely done (50, 51). 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). Without the screening blood test, PA is almost impossible to diagnose due to the absence of specific symptoms and signs other than high BP. Lack of diagnosis or delayed

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).

diagnosis of PA is associated with poor BP control, high burden of symptoms, and poor quality of life (QOL) (3, 4) and results in increased morbidity and mortality (1, 2, 7, 69).

Once diagnosed, PA has specific treatment that differs from that of primary hypertension. The source of excess aldosterone from a unilateral adrenal adenoma can be removed surgically, leading to a potential cure of hyperaldosteronism, or the actions of aldosterone can be specifically blocked by MRAs. The elevated risk of cardiovascular events is ameliorated in individuals with PA treated with unilateral adrenalectomy or sufficient dose of an MRA (7). Numerous studies demonstrate that specific treatment is able to improve cardiovascular and renal outcomes in individuals with PA (see Question 2 (7-9, 32). This highlights the importance of early detection of individuals with PA who can benefit from targeted medical or surgical treatment that would not be applied if individuals remained undiagnosed and instead treated as having primary hypertension.

Early screening for PA has also been demonstrated to be cost-effective in studies from Japan, China, and Australia (70-72). It is also favored by primary care clinicians (73) and desired by patients (74).

The screening test for PA has varying diagnostic accuracy, depending on the decision threshold adopted by individual centers. By the nature of screening, the threshold is usually set lower to permit high sensitivity at the expense of lower specificity (ie, more false-positive results) (75).

A false-positive screening blood test could lead to a cascade of unnecessary investigations, but PA can generally be excluded by the next diagnostic step with aldosterone suppression testing. However, even if the individual is initiated on an MRA on the basis of a false-positive screening test, MRA treatment may still benefit individuals with an elevated ARR (typically due to a low or suppressed renin) for a few reasons. First, a systematic review and meta-analysis demonstrated that MRAs are superior to routine antihypertensive therapy (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) in treating low-renin hypertension, which is the typical diagnosis given to individuals with suspected PA who do not meet current diagnostic criteria for PA (76). Second, 20% of individuals with a positive ARR screening test but a negative aldosterone suppression test (ie, false-positive screening test) may develop PA over time (77). Third, low renin levels and high ARRs are predictors of BP response to MRA treatment, even in individuals without a formal diagnosis of PA (19).

Evidence to Decision Factors

As described in the Introduction, the panel also used the Evidence to Decision (EtD) framework for this and all subsequent Questions, to consider broader factors such as stakeholder values and preferences (including insights from clinical experts and patient representatives), costs and resources required, cost-effectiveness, acceptability, feasibility, and the potential impact on health equity.

PA screening requires commonly available and relatively low-cost laboratory tests (aldosterone and renin measurements). However, downstream testing—such as aldosterone suppression tests, adrenal imaging, and adrenal vein sampling (AVS)—introduces significant additional costs and is not universally available, particularly in resource-limited settings. While initial screening is affordable at the individual level, implementation of universal screening will increase overall healthcare system costs due to follow-up testing, specialist referrals, and potential surgical interventions.

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. While upfront screening costs are higher when applied broadly compared to targeted screening of high-risk groups, modeling studies demonstrate that screening remains below commonly accepted willingness-to-pay thresholds. In addition to general population studies, cost-effectiveness has been demonstrated in specific high-risk groups, such as individuals with resistant hypertension or those with obstructive sleep apnea, where screening prevents cardiovascular complications and reduces long-term healthcare expenditures. The degree of cost-effectiveness, however, varies across healthcare settings.

For the impact of screening on equity, the panel considered that PA is underdiagnosed globally, particularly in underserved populations and minority groups, contributing to health disparities in hypertension-related outcomes. Limited access to screening, confirmatory testing, and specialized care—especially in rural and resource-poor settings—delays diagnosis and treatment. PA screening may reduce disparities by improving detection; however, inequities could be exacerbated if follow-up services, such as subtype diagnosis and AVS, remain inaccessible to disadvantaged populations. The

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
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
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.

panel judged the impact on equity as mixed, taking into account pragmatic treatment pathways provided in Fig. 2 that permit targeted treatment for PA without extensive testing.

The panel judged that acceptability of PA screening will vary among providers. Primary care clinicians, in particular, may have lower acceptance due to limited awareness of PA, difficulties interpreting results in patients on interfering medications, and concerns about the complexity and availability of subtype testing. Some also view medication washout as burdensome or potentially risky. In contrast, screening is generally well-accepted by patients, especially at the time of initial hypertension diagnosis. However, provider hesitancy could limit implementation, particularly in settings with high workloads or limited specialist access.

The panel judged that the feasibility of PA screening will vary by setting and stakeholder perspective. While screening relies on simple, widely available biochemical tests and is technically feasible, implementation has remained low. This is

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.

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.

likely due more to the complexity of prior diagnostic algorithms than to challenges with performing the tests themselves. The current guideline offers suggestions for more pragmatic and feasible approaches to PA testing and treatment (Figs. 1-3).

Justification for the Recommendation

The panel suggests PA screening for individuals with hypertension based on the high prevalence of PA, its underdiagnosis, and the potential to reduce cardiovascular morbidity and mortality through targeted treatment. However, this is a conditional recommendation, reflecting important limitations in the evidence base.

The certainty of evidence for both benefits and harms is low, primarily due to reliance on indirect data and observational studies. While existing evidence suggests improved BP control and reduced long-term complications with screening, the magnitude of benefit remains uncertain. No direct comparative studies between screening and no screening were identified for critical clinical outcomes.

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.

The panel also acknowledged feasibility concerns, particularly the burden on healthcare systems and specialist services, especially in primary care and resource-limited settings. Therefore, the recommendation emphasizes that implementation should be context-sensitive, depending on available resources, local expertise, and healthcare system capacity. It also underscores the need for additional guidance to help clinicians interpret and manage screening results, especially when interfering medications are present.

Ultimately, this conditional recommendation supports screening to improve PA detection and treatment but leaves room for adaptation based on local resources, feasibility, and priorities. The panel judged that, on balance, the likely benefits outweigh the harms but that the recommendation should be applied flexibly.

Implementation Considerations

This is a conditional recommendation, and its implementation will vary depending on contextual factors at both the healthcare system and clinician-patient levels.

Health system–level considerations

When healthcare systems consider implementing this conditional recommendation, they must weigh several interconnected factors that will shape feasibility, sustainability, and equity. Expanded PA screening may improve detection but will also introduce system-level demands that vary depending on resources, infrastructure, and workforce capacity. Key considerations include:

Resource availability. Availability of laboratories to conduct aldosterone, renin, and potassium testing, as well as capacity for downstream evaluations such as aldosterone suppression testing, adrenal imaging, or AVS, varies widely. In settings where advanced diagnostics or specialist services are limited, alternative approaches—such as empiric MRA therapy following a positive screening result—may be appropriate.

Infrastructure and workflow integration. The ability to integrate PA screening into existing hypertension care pathways will depend on clinical workflow structures and system-level coordination between primary care and specialty services. This includes managing referrals, follow-up testing, and treatment decisions following abnormal results.

Financial and equity considerations. Widespread screening may increase healthcare costs, particularly when considering downstream diagnostics and treatment. Equity concerns are particularly relevant in rural and underserved regions, where infrastructure may be lacking and specialist access is limited. Mitigating strategies could include developing regional referral hubs, streamlining diagnostic algorithms, or creating context-sensitive care pathways that balance feasibility and effectiveness.

Provider training and system support. Successful implementation requires investment in education for primary care clinicians and other front-line providers on PA screening protocols, including management of interfering medications and appropriate referral thresholds.

Clinician- and patient-level considerations and implementation tools

At the clinician and patient level, implementation is shaped by knowledge, attitudes, and available decision-support tools. Clinicians may be hesitant to adopt screening due to limited familiarity with PA, perceived testing complexity, or concerns about managing false positives and interpreting results in patients on interfering therapies. To address this, the guideline provides practical tools—including Figs. 1 and 2—to streamline clinical decision making, guide result interpretation, and clarify pathways for management or referral based on patient characteristics and available resources.

Additional implementation considerations include:

- Some panel members consider every hypertensive individual with low renin levels as affected by PA. Despite almost all individuals with PA having low renin concentration or activity, a number of individuals with low renin do not have PA (eg, individuals with high salt intake or Liddle syndrome), hence a nonsuppressed aldosterone concentration should be required together with low renin to consider the individuals at risk of PA.
- 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). 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. The approach for subsequent investigations or pragmatic therapy with MRA should be weighed in individual evaluation.
- 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.

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Determining the benefit of MRA treatment (vs other nonspecific antihypertensive treatments) in individuals with an increased ARR but a negative aldosterone suppression test
- Determining the efficacy of nonsteroidal MRAs and aldosterone synthase inhibitors compared with spironolactone in individuals with PA and in those with low renin or an elevated ARR who do not meet the current diagnostic criteria for PA
- Evaluating the efficacy and cost of novel strategies for screening outside the ARR (eg, steroid profiling, omic signatures, clinical scores, and machine-learning methods (82, 83)
- Conducting a gold-standard prospective randomized controlled trial (RCT) in which individuals with newly diagnosed PA are randomized to treatment with standard medical therapy vs PA-specific medical therapy in order to assess cardiovascular outcomes (however, for ethical reasons, this study is not likely to be undertaken)

Treatment of Primary Aldosteronism: Specific vs Nonspecific Therapies

Background

Specific therapies directed against aldosterone excess are available: treatment with mineralocorticoid receptor antagonists (MRAs) and, if appropriate, unilateral adrenalectomy (84, 85). If those therapies result in better outcomes than nonspecific antihypertensive therapy, encouraging their implementation among hypertensive individuals with PA is appropriate.

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 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 antihypertensive therapy.

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/LGYDlKeCN6A.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 2 decision making: 1) percent of individuals achieving blood pressure (BP) control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) major adverse cardiovascular events (MACEs), 6) atrial fibrillation, 7) stroke, 8) ischemic heart disease, 9) heart failure, 10) cardiovascular mortality, 11) all-cause mortality, and 12) adverse events.

Our systematic review yielded only 2 studies, both of which were observational in nature. One (4) showed that (a) all individuals who underwent unilateral adrenalectomy displayed complete biochemical resolution of PA at 6-month follow-up assessment; (b) individuals receiving an MRA showed a reduction of SBP and diastolic BP (DBP) without a significant increase in antihypertensive treatment; (c) individuals with primary hypertension treated with nonspecific antihypertensive agents showed SBP and DBP reductions at 6 months but with increased treatment.

Due to the limited availability of studies directly evaluating the comparative effectiveness and potential harms of PA-specific treatment vs nonspecific hypertension management, this recommendation also relies on indirect evidence. This indirect evidence derived from noncomparative observational studies. Individuals with PA who are not receiving PA-specific therapy demonstrate higher rates of cardiovascular, cerebrovascular, and renal complications than do individuals with primary hypertension and an otherwise similar risk profile (1, 2). This excess risk is abrogated, and quality of life (QOL) improved following the institution of PA-specific medical or surgical treatment (7, 86). Individuals with PA who undergo surgery demonstrate a lower rate of cardiovascular and cerebrovascular complications than do matched individuals (based on BP and cardiovascular risk profile) with primary hypertension (7). Individuals with bilateral PA undergoing sufficient MRA therapy to unsuppress renin, display a similar (rather than higher) risk to matched individuals with primary hypertension, whereas individuals treated with MRA therapy in doses that are insufficient to unsuppress renin still display increased risk (7).

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).

In summary, this indirect evidence shows that institution of specific treatment (medical or surgical) in individuals with PA results in a significant improvement of hypertension control. BP normalization occurs in a significant proportion of those who undergo surgery for lateralizing forms of PA (89). Furthermore, therapies (medical or surgical) that directly target the increased aldosterone in PA reduce the excess cardiovascular, cerebrovascular, and renal complications associated with PA.

Spironolactone's dose-dependent side effects (including gynecomastia, erectile dysfunction, and menstrual irregularities) limit the efficacy and tolerability of this medication in PA. However, newer MRAs, such as eplerenone, have a much lower side effect profile (see Recommendation 9). Surgical therapy requires skilled surgeons and adequate postsurgical care to minimize surgical complications.

Evidence to Decision Factors

- Costs of medical therapy are minor (in the case of spironolactone) to moderate depending on the medication used, whereas costs of surgical therapy vary.
- Three health economic studies in Japan, Australia, and China demonstrated cost-effectiveness of screening for PA in the general hypertensive population. Cost-effectiveness was mainly due to a decrease in lifelong complications and their associated costs in individuals with PA who received PA-specific therapy compared with those who did not receive therapies targeting PA (70-72).
- Surgical therapy requires skilled surgeons and adequate postsurgical care and has economic consequences for individuals.
- Medical therapy requires individualized titration and surveillance through regular follow-up visits. In areas where these resources are available, the intervention should be feasible.
- Specific medical or surgical treatment of PA should be accepted by individuals since it represents targeted therapy, improved hypertension control (and sometimes cure), improved QOL, and a reduction in the complications associated with PA.
- While PA-specific therapy is likely to be acceptable to primary care clinicians, the steps required to identify individuals with PA who are candidates for specific surgical or medical treatment may reduce acceptance (and, hence, uptake) because of:
  1. lack of knowledge of prevalence and complications of PA;
  2. lack of familiarity with implementing and interpreting screening tests;
  3. lack of familiarity with using MRAs; and
  4. costly, invasive, and challenging procedures associated with subtype diagnosis (lateralizing vs bilateral adrenal aldosterone production) for individuals contemplating potential unilateral adrenalectomy.
- Finally, the diagnosis of PA and treatment with MRA should be affordable in most clinical settings. Subtype diagnosis, especially when using adrenal vein sampling (AVS), and access to surgical intervention may be limited in some settings. After years of implementation with high fidelity, equity will probably be increased.

Justification for the Recommendation

Aldosterone excess has adverse cardiovascular and renal effects that go above and beyond the effects of hypertension, leading to a higher rate of cardiovascular and renal complications in individuals with PA compared with individuals with primary hypertension matched for BP levels. Unilateral adrenalectomy in individuals with lateralizing forms of PA often leads to cure of hypertension, and surgically treated individuals demonstrate a lower rate of cardio- and cerebrovascular complications than do matched (for BP and cardiovascular risk profile) individuals with primary hypertension. Individuals with PA treated with MRAs in sufficient doses to unsuppress renin demonstrate a similar (rather than higher) risk to matched individuals with primary hypertension. While the certainty of evidence is low, indirect data from noncomparative cohorts support the intervention,

as the benefits observed with all therapies for PA are likely to outweigh the associated harms.

The panel also considered the economic implications of PA-specific therapies. While medical therapy has negligible costs, surgical treatment is associated with higher and variable costs depending on the country and health care system. Nonetheless, cost-effectiveness analyses generally favor PA-specific therapies. The panel concluded that the acceptability and feasibility of implementing these therapies depend on available resources and clinical expertise.

Given the overall certainty of the evidence regarding benefits and harms and recognizing that the implementation of PA-specific therapies varies by context, the panel issued a conditional recommendation for the use of PA-specific therapies over nonspecific antihypertensive treatments. This recommendation reflects the balance of evidence, contextual considerations, and resource variability across different settings.

The risk of MRA side effects can be minimized by commencing at low doses (eg, 12.5-25 mg of spironolactone daily) and increasing the dose gradually (eg, every 2-3 months or sooner if clinically indicated) as required to control BP (see Question 9. Table 10, Fig. 3).

Measurement of renin during MRA titration can assist in treatment decision making, but this is less straightforward if the individual is on other medications that affect renin levels (see Question 7).

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Assessing health equity after implementation of this recommendation
- Assessing efficacy and safety of newer nonsteroidal MRAs and aldosterone synthase inhibitors in the medical treatment of PA and developing new medications
- Conducting comparative effectiveness studies to assess PA-specific therapies (both medical and surgical) against nonspecific antihypertensive treatments in diverse clinical contexts and subgroups
- Studying the barriers to widespread adoption of PA-specific therapies, including clinician knowledge gaps, individual preferences, and logistical challenges associated with identifying lateralizing vs bilateral aldosterone production and treatment access
- Establishing large, diverse, and prospective cohorts to monitor long-term outcomes of PA-specific therapies, including cardiovascular and renal events, QOL, and cost-effectiveness
- Investigating disparities in access to PA-specific diagnostic and therapeutic interventions, particularly in low-resource settings and regions with limited access to AVS, surgical expertise, and newer medications

Screening for Primary Aldosteronism in Individuals With Hypertension

Background

Screening for primary aldosteronism (PA) allows for early identification and treatment, which can improve patient outcomes (Question 1). Several strategies exist for PA screening, with the most used approach being the measurement of aldosterone and renin (concentration or activity) and calculation of the aldosterone to renin ratio (ARR). This method may be more sensitive than relying solely on 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.

However, there are practical challenges to using aldosterone and renin for screening. The accuracy of these measurements can be influenced by medications, dietary sodium, and sampling conditions, which may lead to false positives or negatives. Additionally, the availability and cost of testing could limit the feasibility of widespread screening. In contrast, hypokalemia is simpler to detect, but screening for hypokalemia may miss many cases of PA, especially milder forms of the disease.

Given these considerations, the guideline evaluates whether measuring aldosterone and renin (including ARR) is a better strategy for screening for PA compared with relying on the detection of hypokalemia alone in individuals with hypertension.

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 a 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.
- Manage interfering medications depending on individual safety and feasibility. The Guideline Development Panel (GDP) outlined both minimal-withdrawal and no-withdrawal strategies of interfering medications before screening (Tables 6 and 7, Fig. 1).
- A positive screen meets both of the following conditions in most circumstances:
  1. Renin is low/suppressed (hallmark of the 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)
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 show ARR cut points for differing assays and units)

- 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 it is 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 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.
- 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.
- 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 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

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/qFJ3iuy78Bw.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 3 decision making: 1) accuracy of PA detection, 2) detection of lateralizing PA, and 3) adverse events.

The systematic review found no studies that directly compared detection rates for PA among individuals screened by serum or plasma potassium levels vs those screened by measuring serum/plasma aldosterone and renin. Therefore, we relied on indirect evidence on the frequency and accuracy of PA detection from observational studies among those with hypertension and hypokalemia vs hypertension and normokalemia. In a retrospective evaluation of the diagnosis of PA from 5 continents, after the widespread use of the ARR as a screening test in individuals with hypertension, identification of PA increased 5- to 15-fold (90). Only between 9% and 37% of individuals had hypokalemia. Three other prospective studies totaling 5797 individuals referred to hypertension centers or from primary care settings reported that only 25% to 30% of those with confirmed PA had hypokalemia (34, 37, 91). 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. Nevertheless, in a study of 95 individuals with lateralizing PA, more than 90% had suppressed renin preoperatively (92). In contrast, 62% to 67% had hypokalemia requiring potassium supplementation preoperatively, suggesting that relying on hypokalemia to detect PA would miss a substantial percentage of individuals with surgically curable PA.

Although the evidence demonstrated that a large proportion of individuals with PA do not have hypokalemia, and thus the ARR would be more sensitive than the presence of hypokalemia, these data were indirect and were mostly derived from selected populations of individuals referred to hypertension centers. Therefore, the level of certainty was low.

In addition to increasing case detection, the ability of the ARR to limit false positives and negatives was another important consideration. The accuracy of detection of PA using ARR has inherent variability as assays, screening conditions, and patient populations are heterogenous, which can affect the screening test's sensitivity and specificity. A meta-analysis of 9 studies (974 individuals) determined that the sensitivity and specificity of the aldosterone to PRA and aldosterone to DRC ratios were reasonable and improved when interfering medications were withdrawn (93). Regarding false negatives, in a study of 216 individuals with PA with at least 2 aldosterone levels drawn (MRAs were withdrawn prior to testing, but other interfering medications permitted), a lower aldosterone concentration cut point of 10 ng/dL was associated with false-negative rates for PA screening of 14.3% for a single aldosterone measurement, and 4.6% for 2 aldosterone measurements (94). Although one meta-analysis (95) demonstrated good overall accuracy, significant variability precludes a single standard cutoff for detecting PA, and false negatives may result.

Evidence to Decision Factors

- The GDP considered that measuring aldosterone and renin has low cost and resource implications, making this an attractive screening tool in most regions.
- Cost studies across multiple countries indicate low cost of the aldosterone, renin, and potassium measurements.
- Three health economic studies in Japan, Australia, and China demonstrated cost-effectiveness of screening for PA in the general hypertensive population, mainly due to reduced costs of lifelong complications related to untreated PA (70, 71, 72).
- The GDP expects that measuring aldosterone and renin should not have a significant impact on health equity, with the caveat that current access to PA screening and to specialists in PA to interpret findings for management varies.
- Although not well studied, available evidence suggests that those living in rural areas and far from tertiary care centers are less likely to be screened with aldosterone and renin (51, 96). With increased clinician and public awareness, testing should increase in these areas.
- A significant barrier to screening is the lack of feasibility of aldosterone and renin testing by clinicians. Complex testing requirements, in particular withdrawal of interfering medications prior to testing and selecting specific subpopulations for screening, underlie some of the poor detection rates (97). Although withdrawing interfering medications is associated with more consistent and increased accuracy of the ARR, several studies indicated that the ARR retained reasonable accuracy with minimal withdrawal or no withdrawal of interfering medications (98, 99).
- The GDP considered that screening for PA in individuals with newly diagnosed hypertension with an estimated prevalence of PA of 2% to 6% prior to medication initiation would be feasible, facilitate widespread screening, and limit false negatives or positives.
- As described in technical remarks, Fig. 1, and Tables 5 and 6, the GDP created a pathway for clinicians to test individuals on antihypertensive medications with minimal or no withdrawal of interfering medications.

Justification for the Recommendation

Screening with serum/plasma aldosterone and renin was selected over hypokalemia as the global screening tool for detecting PA based on indirect evidence that PA is more common than previously appreciated and that most individuals with PA do not have hypokalemia. Limiting screening to individuals with hypokalemia would miss many cases requiring PA-specific therapy, some with potential for cure, and they would remain at increased risk of cardiovascular and renal events. However, screening with serum/plasma aldosterone and renin has notable limitations. The accuracy is variable and depends on assay type; can be influenced by individual sodium intake/volume status, medications (Tables 6 and 7), and other factors; and has inherent intra-individual variability. Despite these limitations, it is a more sensitive screening tool than hypokalemia, has reasonable accuracy overall with or without interfering medications, and is widely available across regions at low cost.

Given the poor uptake of screening for PA and missed opportunity to provide targeted treatment for individuals with PA, the GDP developed several implementation strategies to facilitate aldosterone/renin screening in primary care settings. Screening with aldosterone and renin in individuals with newly diagnosed hypertension prior to medication start is highly feasible with a more straightforward interpretation. Withdrawing a minimum set of interfering medications or not withdrawing them are also screening options for individuals on antihypertensive therapy and should improve the practicality of PA screening especially when medication withdrawal is not practical or safe.

Other approaches for screening include only screening renin or measuring 24-hour urinary excretion of aldosterone. However, these strategies do not have sufficient evidence or cost-effectiveness data to justify their use for widespread screening. Also, some individuals with low renin do not have PA (ie, those with high sodium diet or Liddle syndrome); thus, to be diagnosed with PA, individuals should have both a suppressed renin and a nonsuppressed aldosterone.

Implementation Considerations

Given that case detection is currently so low (67), and detecting cases of PA would lead to targeted therapy that would improve BP control and cardiovascular morbidity, and cure hypertension in some cases, high priority was given to increasing the sensitivity of case detection while maintaining reasonable specificity.

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Conducting prospective studies to refine the thresholds for the ARR and absolute aldosterone concentration across diverse patient populations and laboratory assays, particularly those using LC-MS/MS for aldosterone measurement

- Investigating novel or other methods of screening for PA, including development of new biomarkers (see Question 4) and assessing 24-hour urine aldosterone
- Investigating the impact of medication withdrawal protocols on false-positive and false-negative rates and developing standardized approaches for testing under real-world conditions, such as minimal or no medication withdrawal

Role of Aldosterone Suppression Testing

Background

The recommended approach to diagnosing PA has generally been a two-step process involving an initial "screening" step (using a plasma/serum aldosterone and renin with calculation of the aldosterone to renin ratio [ARR]) followed by a second "confirmatory" step to either confirm or exclude the diagnosis (using an aldosterone suppression test). However, the value of the confirmatory aldosterone suppression test remains uncertain because it is still unclear whether performing an aldosterone suppression test significantly improves the detection of PA or reduces false-positive results following an initial positive screening. It is also unclear whether this additional step has any direct impact on important clinical outcomes, such as improved BP control or reduced cardiovascular risk, after treatment with either medical or surgical interventions for PA, and prediction of lateralizing PA. Given these uncertainties, the guideline addresses whether care guided by aldosterone suppression testing should be used in individuals with a positive PA screening result, before initiating further diagnostic steps and/or specific treatment for PA, or if treatment can proceed without confirmatory testing.

Question 4. Should care guided by aldosterone suppression testing vs no aldosterone suppression testing be used in individuals with a 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):

- In individuals with resistant hypertension or hypertension with hypokalemia and overt biochemical evidence of renin-independent aldosterone production (direct renin concentration [DRC] <2 mU/L or plasma renin activity [PRA] <0.2 ng/mL/h and plasma aldosterone concentration >20 ng/dL [>554 pmol/L] via immunoassay or >15 ng/dL [>416 pmol/L] via liquid chromatography–tandem mass spectrometry [LC-MS/MS] assay), aldosterone suppression testing is not recommended due to the risk of false-negative results, which may exceed the risk of false-positive screening results.
- Individuals unwilling or unable to pursue adrenal venous sampling (AVS) 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.
- 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.
- 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 <~11 ng/dL [<~305 pmol/L] [immunoassay] or <~8 ng/dL [<~222 pmol/L] [LC-MS/MS]).

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/DF0l5-vIoxI.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 4 decision making: 1) accuracy of PA detection, 2) detection of lateralizing PA, 3) percent of individuals achieving blood pressure (BP) control, 4) number of antihypertensive agents, 5) dosage of antihypertensive agents, 6) systolic BP (SBP) level, and 7) adverse events (eg, for medications, invasive procedures, surgery, aldosterone suppression tests).

We found no RCTs that addressed this question. Likewise, no prospective and head-to-head studies are available evaluating the value of aldosterone suppression testing, in addition to screening results, on treatment outcomes in PA. Therefore, the panel's recommendation relied primarily on evidence derived from retrospective observational studies. The systematic review found only one study (retrospective observational study) that was included (24). Cornu et al showed that when conducting the saline suppression test (performed in the supine position) in individuals with high-probability features of PA, all of whom underwent AVS, even very low post-saline aldosterone levels (<139 pmol/L or 5 ng/dL) could not definitively exclude lateralizing PA (24). Similarly, another study showed that lateralizing PA could be detected in 15% of individuals with a post-supine saline suppression test aldosterone below 10 ng/dL (25); in general, the degree of nonsuppressibility in this study correlated with the likelihood of lateralization of

AVS, thereby providing a desirable prognostic value. However, the choice of protocol and aldosterone assay are factors that can modify the interpretation of the results. For example, the sensitivity of the saline suppression test at predicting the fludrocortisone suppression test has been shown to be superior when conducted in the seated position vs the supine position (100). Moreover, the use of modern LC-MS/MS aldosterone assays yield lower aldosterone values than traditional immunoassays, thereby warranting a re-assessment of aldosterone interpretations for virtually all aldosterone suppression tests (101-105).

Two systematic reviews and meta-analyses (106, 107), including 55 and 31 studies respectively, concluded that the accuracy of aldosterone suppression tests in confirming PA was overestimated and that the number of missed cases (false-negative interpretations) may exceed the number of overdiagnoses (false-positive interpretations) (106). These results were attributed to inflation of diagnostic accuracy due to biased selection of individuals with very high probabilities of having PA. One study reported the anecdotal experience of a hypertension referral center abandoning the use of aldosterone suppression tests entirely from the diagnostic cascade for individuals with high-probability features of PA (ie, hypertension with a high ARR or hypertension with hypokalemia) over a period of 6 years (2005-2011) (108). When using just the screening aldosterone and renin values to guide subsequent decisions, the authors estimated that less than 3% of individuals were at risk of a false-positive diagnostic interpretation.

False-negative determinations after an aldosterone suppression test in individuals with high-probability features of PA is considered to be a substantial undesired effect (23-26). If aldosterone suppression testing is used to enhance knowledge of lateralization and AVS use, the risk of undesirable effects is low. However, a negative aldosterone suppression test does not preclude the option of commencing specific medical therapy for PA, which has shown to be effective in individuals with low-renin hypertension and renin-independent aldosterone production even when they do not meet the formal diagnostic criteria for PA (19-22). For example, in one study evaluating the captopril challenge test, aldosterone-directed therapy was highly effective at improving biochemical and clinical outcomes even for patients that did not meet the formal diagnostic criteria for PA (26).

Evidence to Decision Factors

- An aldosterone suppression test is cost-effective in the long term, particularly if it assists in identifying lateralizing forms of PA that might guide curative surgery. The cost and resources will depend on the test used.
- Although no specific studies address this aspect, aldosterone suppression testing appears acceptable by clinicians with expertise in PA, as well as by patients. In a limited-resource setting, conducting aldosterone suppression testing may be less acceptable.
- Aldosterone suppression testing can be prohibitively costly or resource-intensive in certain places. As a result, many parts of the world favor aldosterone suppression tests that are less expensive and resource-intensive, whereas other resource-rich institutions rely on more laborious and costly aldosterone suppression tests. This discrepancy further adds to implications for equitable health care delivery.

Justification for the Recommendation

At least 10 aldosterone suppression testing protocols have been described and used to confirm or exclude PA, 4 of which are widely recommended by prior major society guidelines (84, 109-111), and each with their own unique thresholds to interpret a confirmation, or exclusion, of a PA diagnosis. These tests include, but are not limited to, fludrocortisone suppression, oral sodium suppression, supine and seated saline infusion, captopril challenge, losartan, dexamethasone-captopril-valsartan, intravenous (IV) furosemide upright, oral furosemide, and posture stimulation tests. Given the heterogeneity and lack of standardization across these tests, the ability to provide general recommendations for their implementation and interpretation is limited. Table 8 describes the 3 most widely used aldosterone suppression tests. Aldosterone suppression testing has traditionally been used to confirm or exclude the diagnosis of PA. Limitations of using aldosterone suppression testing as a diagnostic metric include that the numerous protocols are not calibrated against one another, and each has diagnostic thresholds that are not validated against a gold standard. The summary of many studies suggests that a single optimal threshold for most aldosterone suppression tests does not exist and that over-reliance on these tests may result in erroneous exclusion of PA cases rather than increased accuracy of diagnosis. The balance of evidence (106, 107) suggests that the quality of evidence to support the accuracy of this practice is low, particularly in relation to confidently excluding the diagnosis. However, if testing results that fall below protocol thresholds are interpreted as implying nonlateralizing PA or low-renin hypertension and prompting initiation of MRA therapy (25, 26, 100), the use of aldosterone suppression testing could serve as both a diagnostic and therapeutic tool. The caveat for this approach is the implicit assumption that a positive PA screen indicates a high pretest probability for PA.

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. Caveats to this approach include its lack of quantifiable metrics to guide such interpretations, supporting data are not uniformly available for all suppression tests/protocols, and high-quality comparative effectiveness studies to assess whether other biomarkers may have similar predictive power are also lacking. Nevertheless, this approach may help some clinicians streamline referrals for AVS, especially when this resource is not readily available, for those who need it and spare those who do not.

Given the low certainty in the trade-offs between benefits and harms of aldosterone suppression testing, along with considerations regarding the costs, resource requirements, and expertise needed to perform it, as well as its feasibility, acceptability, and equity implications, the panel suggests conducting aldosterone suppression testing in individuals with an intermediate probability for lateralizing PA who desire to pursue eligibility for surgical therapy (Fig. 2). Aldosterone suppression testing can be performed without stopping or changing antihypertensive medications as long as renin is low; when treatment with MRAs has been initiated and renin is no longer low, it is advised that these medications be stopped, and aldosterone suppression testing be performed only when renin is low again.

Comments

The use of aldosterone suppression testing in individuals with a positive PA screen may best serve individuals and clinicians by providing them with a probabilistic framework to determine the optimal treatment pathway (Fig. 2). The evidence for the outcomes of the percentage of individuals achieving BP control and detection of lateralizing PA following aldosterone suppression testing was very low. However, conducting relatively safe testing to prognosticate the value of undergoing AVS (and determining the next therapeutic steps) would likely be valuable to individuals.

In resource-constrained settings, aldosterone suppression testing may be difficult to implement, considering the lack of evidence for major outcomes.

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Prospective, randomized, comparative outcome studies: The lack of a gold-standard diagnostic to define PA is one of the main reasons why aldosterone suppression tests are not uniformly calibrated to one another or validated against a central benchmark. As a result, most available evidence provides low-quality information to reliably adjudicate whether the use of aldosterone suppression testing is superior to no aldosterone suppression testing. Prospective studies, employing randomization to each approach, and evaluating clinical efficacy outcomes are needed to robustly assess whether the practice of aldosterone suppression testing adds value in selecting the correct individuals for localization procedures and targeted treatment, and improves outcomes.
- New diagnostic biomarkers: Novel cutting-edge omics technologies together with the application of artificial intelligence (AI) for disease prediction hold potential for the development of more effective biomarkers to diagnose PA. Besides the improved diagnostic performance of plasma or urinary steroid profiling to diagnose PA (82, 114), a recent approach using multi-omics data, including plasma miRNAs, plasma catechol O-methylated metabolites, plasma steroids, urinary steroid metabolites, and plasma small metabolites, integrated by machine learning, was able to correctly diagnose PA with high sensitivity and specificity distinguishing them from individuals with primary hypertension or other forms of endocrine hypertension (83). This and similar approaches, combining clinical data with biologic profiles, may provide better performances to diagnose PA and potentially lateralizing PA, thereby possibly eliminating the need for aldosterone suppression tests in the future.

Medical Therapy vs Surgical Therapy for Individuals With Primary Aldosteronism

Background

Effective prevention of excess cardiovascular and cerebrovascular risk in individuals with primary aldosteronism (PA) involves targeted therapies for lateralizing and bilateral forms of the disease. For individuals with bilateral disease and those who do not desire or are not a candidate for surgery, lifelong pharmacotherapy with a mineralocorticoid receptor antagonist (MRA) is the standard approach. In contrast, surgical intervention is typically recommended for individuals with lateralizing PA who wish to pursue this option. However, surgical intervention requires adrenal venous sampling (AVS) to confirm lateralization, a procedure that demands significant expertise and specialized resources, often limited to tertiary care centers. These challenges highlight the need to balance the benefits and feasibility of medical vs surgical treatments. Considering these factors, the panel formulated this question to determine the best management strategy for individuals with PA.

Question 5. Should primary aldosteronism–specific medical therapy vs surgical therapy be used in individuals diagnosed with 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 (Fig. 2):

- 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 an 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 decline the surgical option or who are not surgical candidates (Fig. 2).
- Individuals with mild PA typically have bilateral disease and may bypass AVS, proceeding directly to medical management (Fig. 2).
- Individuals with multiple comorbidities who may not be good surgical candidates may also proceed directly to medical therapy (Fig. 2).

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/FT5oNrFmGsY.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 5 decision making: 1) percent of individuals achieving blood pressure (BP) control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) major adverse cardiovascular events (MACEs), 6) atrial fibrillation, 7) stroke, 8) ischemic heart disease, 9) heart failure, 10) cardiovascular mortality, 11) all-cause mortality, and 12) adverse events.

Systematic review metadata (53) from 4 randomized controlled trials (RCTs) enrolling 669 individuals with PA (mean age 52.6 years, 28.7% females) and from 52 comparative observational studies with 17 893 individuals with PA (mean age 52.6 years, 46.9% females) were included for evidence synthesis.

No significant differences between medical and surgical management were identified for hypertension remission. However, a meta-analysis (53) of 20 observational studies, including 3209 individuals with PA, showed an association of *lower* long-term efficacy in achieving BP control with PA-specific medical therapy compared with surgical therapy (odds ratio [OR]: 0.333; 95% CI: 0.202-0.550). Additionally, long-term SBP levels were higher with medical management in an analysis of 42 observational studies (53) of 10 286 persons with PA mean difference (MD: 4.811; 95% CI: 3.327-6.294).

Observational studies also indicate that medical treatment for PA is associated with a higher number of antihypertensive agents (21 studies, 4998 individuals) and higher dosage of antihypertensive agents (8 studies, 1409 individuals) compared with surgical intervention (MD: 1.339; 95% CI: 1.136-1.542; MD: 1.855; 95% CI: 1.400-2.309, respectively) (53). The higher number of antihypertensive agents with medical treatment was supported by a review of clinical trials including 425 persons with PA (MD: 1.348; 95% CI: 0.866-1.830) (115-117), and the higher dosage of antihypertensive agents associated with medical vs surgical management persisted in an analysis based on lateralizing disease only (MD: 1.733; 95% CI: 1.160-2.306).

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). The increased risk for heart failure and all-cause mortality persisted in a review of metadata based on lateralizing PA only (OR: 2.182; 95% CI: 1.38-3.452 and OR: 2.082; 95% CI: 1.124-3.855, respectively). One cohort study reported that MRA therapy compared with adrenalectomy had a higher risk of mortality, major cardiac or cardiovascular events, and combined new-onset atrial fibrillation with mortality (118). However, this increased risk might be mitigated with adequate mineralocorticoid receptor blockade based on unsuppressed renin activity (9).

Due to off-target androgen receptor antagonism and progesterone receptor agonism, spironolactone has dose-dependent side effects of gynecomastia and sexual dysfunction in men and menstrual irregularities in women (116, 119-121). The meta-analysis of a systematic review of 2 observational studies estimated significantly higher medication-related adverse events with medical therapy compared to surgical therapy (OR: 29.853; 95% CI: 3.726-239.166) (123). Of note, fewer side effects were associated with eplerenone than spironolactone, consistent with eplerenone's greater specificity for the mineralocorticoid receptor (122). While the antihypertensive efficacy of eplerenone was lower than that of spironolactone, the eplerenone doses studied were about one-third less potent than the spironolactone doses.

Therefore, the panel concluded that the balance of effects favor surgery, depending on lateralization of aldosterone hypersecretion, individual choice, and suitability for surgery. Refer to Question 6 for a definition of lateralization.

Evidence to Decision Factors

- 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).
- MRAs are readily available, including in resource-poor settings, whereas surgery requires additional resources.
- MRA treatment is equitable and independent of socioeconomic status with no significant inequality of outcomes (126).
- MRA therapy is often preferred by health care clinicians due to its accessibility and low cost. However, individual adherence to spironolactone is lower compared with other antihypertensive medications, possibly related to its antiandrogen and progestogenic side effects.
- 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.

Justification for the Recommendation

Based on the systematic review and indirect evidence, the panel provided a recommendation for either medical therapy or surgical intervention for the treatment of PA. This recommendation is based on the observed benefits of surgical treatment, including lower SBP, more effective BP control, reduced risk of stroke, fewer MACEs, lower incidence of heart failure, decreased need for antihypertensive medications, improved quality of life (QOL), and lower all-cause mortality. While medical therapy with MRAs showed less favorable outcomes overall, the excess risk of hard outcomes might be mitigated by monitoring treatment response based on an increase in renin rather than the BP response alone (9) (refer to Question 7). However, individuals often favor surgical therapy due to the possibility of avoiding lifelong medical therapy, overall QOL improvements, limited pharmacologic treatment options, and side effects of some MRAs (eg, spironolactone). 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.

For a definition of lateralization, refer to Question 6.

Comments

Individuals managed either medically or surgically should be monitored according to clinical and biochemical outcomes and to ensure clinical safety as recommended by international expert consensuses and in Questions 7 and 9 (85, 86).

Postsurgical outcomes partly depend on successful AVS and the availability of skilled adrenal surgeons, which might be limited outside specialized centers. Preoperative morbidity and length of stay are more favorable in high-volume centers (130).

Adrenalectomy is mainly performed by a laparoscopic approach, but open adrenalectomy can be considered under specific conditions (eg, in individuals who have had multiple prior laparotomies).

Individuals with bilateral PA in whom medical therapy is not well-tolerated or effective can be considered for unilateral adrenalectomy although evidence regarding clinical effectiveness in those situations is limited (131-133).

Research Considerations

Further research is necessary to investigate the protective effects of aldosterone synthase–inhibitor therapy as well as other strategies like adrenal ablation and tailored approaches for milder forms of PA.

Role of Adrenal Venous Sampling and Computed Tomography Scanning in Determining Lateralization of Primary Aldosteronism

Background

Cross-sectional imaging (eg, computed tomography [CT] or magnetic resonance imaging [MRI]) has limitations in the evaluation of individuals with primary aldosteronism (PA) because it cannot determine the functional activity of adrenal glands. This can result in misclassification as lateralizing or bilateral PA, especially in those with bilateral adrenal hyperplasia or nonfunctional adrenal nodules. While adrenal venous sampling (AVS) can improve diagnostic accuracy and guide treatment decisions, its limited availability raises the question of whether its use significantly improves outcomes compared with CT scanning alone. This guideline question addresses whether care guided by adrenal lateralization using both CT scanning and AVS should be preferred over CT scanning alone for directing the treatment approach in individuals with PA.

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.
- 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 >1.0-cm unilateral adrenal adenoma on CT scanning).

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/FL6i3ZvDYXg.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 6 decision making: 1) detection of lateralizing PA, 2) biochemical cure rate post-adrenalectomy, 3) percent of individuals achieving blood pressure (BP) control, 4) number of antihypertensive agents, 5) dosage of antihypertensive agents, 6) systolic BP (SBP) level, and 7) adverse events.

A systematic review of 38 studies including 950 individuals reported that when AVS was used as the criterion standard test for the diagnosis of lateralizing PA, CT/MRI misdiagnosed the cause of PA in 37.8% of individuals (134). Several retrospective studies reported low-level concordance between CT scanning alone and CT scanning plus AVS (89, 135, 136). In individuals who were biochemically cured after surgery with AVS-based management, CT/MRI alone correctly detected lateralizing PA in 58.6% (135) and 64% of cases (89). These studies highlight the limitations of adrenal CT in the diagnosis of unilateral aldosterone-producing adenomas (APAs). Small unilateral APAs may not be visible on CT, leading to misinterpretation as normal adrenal glands. Conversely, apparent microadenomas on CT might actually be areas of hyperplasia, making unilateral adrenalectomy inappropriate. Furthermore, nonfunctioning unilateral adrenal macroadenomas, which are common in individuals older than age 35 years, cannot be distinguished from APAs on CT.

Therefore, to address the performance of adrenal lateralization with CT scanning plus AVS vs CT scanning alone for the management of PA, the systematic review (53) identified one randomized controlled trial (RCT) (117) enrolling 200 individuals with PA (mean age 53.1 years; 21.7% female) and 29 comparative observational studies with 8375 participants (mean age 50.4 years; 48.8% female).

Data from the RCT alone did not show differences in intensity of antihypertensive medications, BP control, or biochemical remission after 1-year of follow-up. Meta-analysis of 4 observational studies including 1070 individuals with PA indicated that compared with AVS-based management, CT scanning alone may be associated with lower postoperative biochemical cure (odds ratio [OR]: 0.266; 95% CI: 0.103-0.690) (89, 137-139). Otherwise, comparable outcomes were observed between AVS- and CT-based management approaches for the detection of lateralizing PA, achieving BP control, number or dosage of antihypertensive medications, and SBP levels.

Additionally, an observational, retrospective, multicenter study reported an overall adrenal vein rupture during 0.61% of AVS procedures, with an inverse correlation between rupture incidence and the radiologist's experience in performing AVS studies (140).

Evidence to Decision Factors

- Resource requirements for AVS include training and time of expert interventional radiologists, accurate laboratory measurements, and interpretation of AVS results (141).
- One RCT reported increased average health care costs for individuals undergoing AVS (117), but decision-tree modeling and incremental cost-effectiveness ratios (ICERs) based on quality-adjusted life years (QALYs) report that AVS-based care is more cost-effective (124, 142).
- AVS has low feasibility to implement due to the requirement for a highly trained interventional radiologist and other additional resources and is probably less acceptable

to care clinicians who do not have local or regional access to a center that performs AVS with a high bilateral adrenal vein cannulation success rate.
- AVS might be unacceptable to some individuals unwilling to undergo an invasive procedure but should be acceptable to individuals who want to achieve hypertension cure and avoid both noncurative surgery based on CT findings alone and lifetime pharmacotherapy.
- AVS has higher costs relative to CT-guided care, is not widely available in most countries, and is offered only in highly specialized centers and not at all in resource-poor countries.
- Although AVS is more accurate than cross-sectional imaging, it is substantially more costly and difficult to implement.
- Individuals with PA prioritize the accurate detection of surgically treatable forms; therefore, AVS is acceptable and desired by those who favor a cure of PA over lifelong mineralocorticoid receptor antagonist (MRA) therapy.

Justification for the Recommendation

The panel recommended that for individuals diagnosed with PA who are candidates for surgical intervention, the treatment approach should be guided by adrenal lateralization using both CT scanning and AVS. This recommendation is based primarily on indirect evidence, and partially supported by direct evidence, highlighting the low detection rate of lateralizing PA with CT scanning alone compared with combined CT scanning and AVS. Also considered was the value that clinicians place on the accuracy of aldosterone lateralization because it leads to successful surgical outcomes in those individuals who want to pursue a surgical cure. 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.

Although a prospective randomized trial reported no apparent outcome differences between CT-based and cosyntropin-stimulated AVS-based management (117), several caveats need to be considered. For example, medication and BP outcome data at 1 year after intervention were pooled from the surgical and medically managed individuals in each arm of the study, which failed to recognize that MRA treatment is a "surgical equivalent." The study was not powered to detect outcome differences in those individuals treated only with surgery based on CT vs AVS. Additional issues with this study included the selection bias toward more florid forms of PA, which limited its generalizability, and a suboptimal selectivity index cutoff for AVS (>3:1 with a cosyntropin infusion-stimulated protocol) that may have led to surgical management in individuals with bilateral adrenal disease in the AVS-based care cohort. In addition, 5 of the 92 individuals in the CT-based management group had apparent unilateral adrenal disease on CT scan but were not managed surgically.

Implementation Strategies

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

Most centers use radiographic contrast administration during AVS to help localize the adrenal veins. Contrast administration carries a risk of a contrast allergy reaction, as does contrast-enhanced adrenal CT. A contrast allergy may necessitate the use of cosyntropin for AVS for those individuals treated with exogenous corticosteroids for contrast-associated allergic reaction prevention (144).

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).

Many groups advocate the use of continuous cosyntropin infusion during AVS to minimize stress-induced fluctuations in aldosterone secretion during nonsimultaneous (sequential) AVS, maximize the gradient in cortisol from adrenal vein to inferior vena cava and thus confirm successful sampling of the adrenal vein, and maximize the secretion of aldosterone from an APA and thus avoid the risk of sampling during a relatively quiescent phase of aldosterone secretion (85, 147-149). 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.

The interpretation of AVS results relies on several key indices and their corresponding cutoff values, which help determine the success of the sampling procedure and the lateralization of aldosterone excess (Table 9). The cortisol concentrations from the adrenal veins and IVC are used to confirm successful cannulation of both adrenal veins. With cosyntropin protocols, an adrenal vein to IVC cortisol ratio (referred to as the *selectivity index*) of more than 5:1 is required to be confident that the adrenal veins were successfully catheterized (141). When cosyntropin is not used, a selectivity index of more than 1.4 to 3.0 is a threshold that has been used to verify successful catheterization (150-152). Use of intraprocedural cortisol measurement has been shown to improve bilateral adrenal vein catheterization success rates (153).

Dividing the right and left adrenal vein aldosterone concentrations by their respective cortisol concentrations corrects for dilutional effects of the inferior phrenic vein flowing into the left adrenal vein and, if suboptimally sampled, of IVC flow into the right adrenal vein catheter. These are termed *cortisol-corrected aldosterone ratios*. With unstimulated or continuous cosyntropin administration, clinicians use a cutoff of the cortisol-corrected aldosterone ratio from high-side to low-side of more than 4:1 (referred to as the *lateralization index*) to indicate lateralizing aldosterone excess (85); a lateralization index less than 3:1 suggests bilateral aldosterone hypersecretion. Individuals with a lateralization index between 3:1 and 4:1 may have either lateralizing or bilateral disease, and the AVS results must be cautiously interpreted in conjunction with the clinical setting, CT scan, and the contralateral suppression of aldosterone secretion.

Although the use of cosyntropin clearly improves the selectivity index, there is debate on its impact on accurate lateralization. In a retrospective cohort study of 340 patients with primary aldosteronism, bilateral simultaneous AVS was performed before and after the administration of cosyntropin (154). Using a lateralization index of >4:1, there was a 19% discordance rate between pre- and post-cosyntropin data sets. More than half (64%) of the discordance was due to apparent lateralizing adrenal disease prior to cosyntropin administration that was reinterpreted as bilateral disease after cosyntropin (154). In the same publication, the authors reported that 10 of 11 similar studies that they reviewed demonstrated either no change or a decrease in lateralization rates following cosyntropin stimulation. Most studies have found no difference in post-adrenalectomy outcomes with or without cosyntropin-stimulated AVS (151, 154, 155) while others found that the post-cosyntropin lateralization index correlated better with positive postoperative clinical outcomes than the unstimulated lateralization index (156).

Finally, in most individuals with lateralizing disease, with cosyntropin-stimulated AVS, the aldosterone to cortisol ratio from the nondominant adrenal vein is lower than the aldosterone to cortisol ratio in the IVC, termed the *contralateral suppression index* (157). When AVS is performed without cosyntropin stimulation, and the aldosterone concentration from the nondominant adrenal is divided by the IVC aldosterone concentration, a cutoff of <2.15 correlates with postoperative clinical outcomes (158). Use of the contralateral suppression index remains controversial and more work is required to validate this and other indices of lateralization.

Comments

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. Antihypertensive agents (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or MRAs) do not interfere with AVS as long as renin is low (159, 160). If renin is not suppressed, changes in the antihypertensive program should be considered before AVS. Drugs that have minimal effect on renin may include selective α_1-receptor antagonists (eg, doxazosin, terazosin, prazosin) and long-acting dihydropyridine (eg, amlodipine, felodipine) or non-dihydropyridine calcium-channel blockers (eg, verapamil, diltiazem).

There are 4 exceptions to the suggested requirement for AVS prior to surgery:

- Most young individuals (eg, age <35 years) who have marked PA (eg, spontaneous hypokalemia, plasma aldosterone concentration >30 ng/dL [>832 pmol/L] by immunoassay or >22.5 ng/dL [>624 pmol/L] by liquid chromatography–tandem mass spectrometry [LC-MS/MS], and suppressed renin), and a unilateral adrenal mass with radiologic features consistent with a cortical adenoma on adrenal CT scan. Adrenal incidentalomas are very uncommon in individuals aged <35 years (0.28%) (161), and marked PA is usually associated with a CT-detectable adrenal nodule (162-164). Thus, in young individuals (eg, age <35 years) with marked PA and a >1.0-cm unilateral adrenal nodule on CT, unilateral adrenalectomy without prior AVS can be considered.
- Individuals with a unilateral adrenal macroadenoma (>1 cm) who have both PA and clinically important cortisol secretory autonomy. The source of clinically important cortisol secretory autonomy is the unilateral adrenal macroadenoma, and a localization study (eg, AVS) is not needed.
- Individuals with familial hyperaldosteronism (types I-IV). These autosomal-dominant disorders are each linked to specific germline pathogenic variants (165, 166). These individuals have bilateral adrenal disease, and AVS is not required (Question 4.) Adrenalectomy is usually not indicated in individuals with familial PA.
- Individuals with primary bilateral macronodular adrenal hyperplasia (PBMAH) who have excessive production of both cortisol and aldosterone (167). These individuals have bilateral adrenal disease, and AVS is not required.

Research Considerations

One of the long-term goals for subtype evaluation is to decrease the reliance on specialized interventional radiologists for AVS. Positron emission tomography (PET)-based imaging with aldosterone synthase–specific molecules is under investigation as a method to identify whether excess adrenal aldosterone production is lateralizing or bilateral (168-170). A recent study showed that pretreatment with dexamethasone converts ^{11}C-metomidate from a nonselective ligand for CYP11B1 and CYP11B2 into an in vivo selective CYP11B2 ligand (171). In 93 patients with PA and CT-detected adrenal nodules who were treated surgically, dexamethasone-suppressed ^{11}C-metomidate PET-CT was noninferior to AVS in diagnosing lateralizing PA (171). In addition, the C-X-C chemokine receptor 4 (CXCR4) is a G protein-coupled transmembrane receptor overexpressed in APAs and exhibits low to undetectable expression levels in normal adrenal tissues and nonfunctional adenomas (172). ^{68}Ga-pentixafor is a radionuclide imaging ligand specifically targeting CXCR4 (173). In 63 patients with PA who were treated surgically, ^{68}Ga-pentixafor PET-CT was noninferior to AVS in diagnosing lateralizing PA (174).

Suppressed vs Unsuppressed Renin in Individuals With Primary Aldosteronism Receiving Primary Aldosteronism–Specific Medical Therapy

Background

Although aldosterone-directed medical therapy has been shown to be beneficial in primary aldosteronism (PA), the optimal approach to dosing and surveillance is uncertain. Whether renin should be used to guide treatment has been considered in prior studies and by consensus groups. The premise of using renin as a biomarker of PA-specific medical therapy stems from the general knowledge of the physiology of endocrine hormone excess (ie, decline in hormone excess or activity is reflected in a rise of the proximal regulatory hormone). Since PA is characterized and diagnosed by aldosterone production despite suppression of renin and angiotensin II, a rise in renin induced by aldosterone-directed medical therapy should reflect the reversal of PA pathophysiology that may portend improved clinical outcomes (175).

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).

Technical remarks:

- 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.

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/EHqkK_8QHm8.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 7 decision making: 1) percent of individuals achieving BP control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) major adverse cardiovascular events (MACEs), 6) atrial fibrillation, 7) stroke, 8) ischemic heart disease, 9) heart failure, 10) cardiovascular mortality, 11) all-cause mortality, and 12) adverse events.

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. There were no statistically significant differences in MACEs (eg, ischemic heart disease, heart failure) in the meta-analysis. In individual retrospective cohort studies, a rise in renin to a level higher than 1.0 ng/mL/h was associated with lower risk for MACEs when compared with persistently suppressed renin (7, 69). In this regard, the addition of renin measurements does not pose a substantial increase in resource utilization. However, the additional costs of measuring renin may be a limiting factor or prohibitive to some clinicians and increase health disparities.

In balance, targeting a rise in renin may be associated with a lower risk of death, stroke, and atrial fibrillation, but the pooled analysis did not demonstrate statistically significant reduction in the risk for MACEs.

Evidence to Decision Factors

- No studies were found that assessed the cost-effectiveness of targeting renin in PA-directed medical therapy.
- There is an obligate cost associated with measuring renin and measuring it frequently during longitudinal care.
- If the studies suggesting that increasing renin with mineralocorticoid receptor antagonist (MRA) therapy can mitigate some of the risk for incident cardiovascular and kidney disease are confirmed or validated, the additional cost of measuring renin is likely to be cost-effective.
- No studies were found that assess the impact of targeting renin in PA-directed therapy on health equity.
- As stated, the costs of measuring renin, in addition to the standard longitudinal follow-up and monitoring for medical therapy for PA, may be a limiting factor for some clinicians (specifically in areas where this test is not readily available).
- No research evidence was identified for acceptability by the health care workers or feasibility.
- Measurement of renin to guide medical therapy is likely feasible at most centers that routinely treat individuals with PA.

Justification for the Recommendation

Because the pathophysiology of PA in most individuals manifests with suppressed renin, a rise in renin with MRA therapy serves as a biomarker indicating a restoration of physiology (ie, sufficient mineralocorticoid receptor [MR] blockade and reduction in extracellular volume) (175). The summary of several observational studies suggests that this practice is associated with statistically lower risks of death and atrial fibrillation as well as a lower number of antihypertensive medications and risk for hypokalemia. Importantly, the primary clinical objective of MRA therapy remains normalizing BP with the fewest number of medications (and normalizing potassium, when applicable); however, achieving a rise in renin is suggested as an additional objective that reflects a better prognosis (175).

Caveats to this approach include that this evidence stems from observational studies susceptible to bias and residual confounding, that there is no direct evidence to dictate what renin threshold to target as optimal, that this approach may not be possible or feasible or necessary in all individuals, that there are different methods to measure renin (activity and concentration) and no consensus on which one is more accurate, and that intensification of MRA therapy to achieve this objective may induce more adverse effects. For these reasons, we suggest focusing on dose intensification of MRA therapy to raise renin, particularly in individuals whose BP is not controlled. Once BP is controlled, non-MRA medications can be lowered or removed, when possible, thus allowing further increases of MRA dosing and attempts to raise renin (Fig. 3). Furthermore, interpretation of renin levels may be hampered in individuals concomitantly receiving other medications that affect renin levels (eg, β-adrenergic blockers that lower renin or renin–angiotensin–aldosterone system [RAAS] inhibitors that may raise renin in synergy with MRAs). Rather than targeting a specific renin threshold, we suggest that the observation that renin has increased from its pretreatment baseline should provide some reassurance of treatment efficacy. Consistent with this recommendation, 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).

Comments

Special populations:

- Individuals with hyperkalemia/chronic kidney disease (CKD) stage 3 and above: Achieving an increase in renin with MRA therapy is challenging in individuals with CKD. The ability to produce and secrete renin may be impaired with advanced CKD and higher MRA doses, which may increase the risk for hyperkalemia. As such, targeting an increase in renin in CKD may not always be a feasible or practical clinical objective. However, since the nonsteroidal MRA finerenone has been shown to reduce adverse cardiovascular and kidney outcomes in 3 large randomized controlled trials (RCTs) of individuals with diabetes and CKD or heart failure (176-178), 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).
- Individuals taking medications that influence renin: The use of some concurrent medications may confound the interpretation of renin. β-Adrenergic blockers can lower renin secretion; therefore, individuals on high doses may not manifest an increase in renin with MRAs. High dietary sodium intake can lower renin, whereas a sodium-restricted diet can increase renin (181); however, most of the global population consumes a relatively high dietary sodium content known to expand intravascular volume and put downward pressure on renin. The use of angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs] and diuretics can raise renin and thereby potentially confound the isolated effect attributable to MRA therapy.

Research Considerations

Current gaps in knowledge call for further research in the following area:

- Conducting prospective, randomized, controlled studies with surrogate outcomes (eg, cardiac imaging, vascular dynamics) and hard outcomes to robustly assess the efficacy of targeting a rise in renin with aldosterone-directed medical therapy

Dexamethasone Suppression Testing in Individuals With Primary Aldosteronism and an Adrenal Adenoma

Background

Assessing cortisol production is considered routine practice in individuals with an adrenal adenoma due to the increased cardiometabolic risks of excess cortisol exposure. In individuals with primary aldosteronism (PA), 24-hour urine steroid metabolome studies and dexamethasone suppression tests indicate that autonomous cortisol secretion (ACS) is not uncommon. Furthermore, excess cortisol production in individuals with PA may affect interpretation of AVS results and/or lead to postoperative glucocorticoid deficiency in those with adenomas co-secreting aldosterone and cortisol.

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

- 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 ACS, measuring plasma metanephrine during adrenal venous sampling (AVS) 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.

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/vRFNnZpoKZY.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 8 decision making: 1) postoperative adrenal insufficiency, 2) ACS detection, 3) false lateralization, 4) AVS accuracy and 5) adverse events. As the systematic review did not identify any studies that directly address this question, additional relevant studies were evaluated.

A number of retrospective cohort studies reported that approximately 5% to 15% of individuals with PA have ACS as defined by a positive 1-mg dexamethasone suppression test with a cortisol concentration more than 1.8 μg/dL (50 nmol/L) (182-186). 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).

Studies have also reported increased cardio-metabolic-renal complications in individuals with PA and concurrent cortisol excess. 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).

In individuals with PA who undergo AVS, studies indicate that ACS may complicate the interpretation of adrenal vein selectivity and lateralization of aldosterone production. Excess cortisol secretion may lead to lateralization of cortisol to

one side with underestimation of aldosterone production, as reflected by the aldosterone to cortisol ratio, on the same side (182, 196, 197). Cortisol production on the contralateral side may be suppressed and lead to the false assessment of inadequate adrenal vein cannulation (196). Current evidence suggests that measurement of plasma metanephrine, which displays minimum fluctuation during stress and a higher adrenal to peripheral gradient compared to cortisol (198, 199), is useful in these cases to assess selectivity and lateralization. Suggested thresholds include selectivity index >12 and lateralization index >4 where metanephrine replaced cortisol in the assessment of selectivity and lateralization (197, 199-203). However, issues with selectivity of adrenal vein catheterization and lateralization of aldosterone production have not been reported in all studies (183), possibly because AVS interpretation was mainly affected in individuals with post-dexamethasone cortisol more than 5 ug/dL (138 nmol/L) (204). One study suggested that AVS performance under cosyntropin stimulation, instead of during unstimulated conditions, may overcome the need to measure metanephrines for the assessment of selectivity and lateralization (197).

For those with concurrent PA and ACS, surgical resection of the adrenal adenoma may lead to postoperative glucocorticoid insufficiency. A study of 108 individuals who underwent unilateral adrenalectomy for a range of reasons reported that 50% of those with concurrent PA and hypercortisolism (n = 12) developed adrenal insufficiency requiring glucocorticoid replacement for a median period of 0.8 months (205).

The potential undesirable effect of performing a 1-mg dexamethasone suppression test may be related to false-positive or false-negative results. False-positive results may lead to unnecessary further investigations, although 24-hour urinary free cortisol and midnight salivary cortisol are noninvasive and relatively accessible tests. More invasive testing would only be conducted if multiple screening tests are positive. The dexamethasone suppression test is considered the most sensitive screening test, and false negatives are uncommon. A meta-analysis demonstrated a sensitivity of 98.6% (96.9%-99.4%), specificity of 90.6% (86.4%-93.6%), positive likelihood ratio of 10.5 (7.2-15.3), and negative likelihood ratio of 0.016 (0.007-0.035) (206). False-positive results can occur due to failure to correctly take dexamethasone, interfering medications such as anticonvulsants and other CYP3A4 inducers that increase dexamethasone degradation, and malabsorption of dexamethasone (207). This issue can be resolved with serum dexamethasone measurement. A range of other conditions may cause false-positive results, including oral estrogen use, obesity, major depression, alcohol use disorder, and acute illnesses. These are covered by guidelines for Cushing syndrome (208).

Evidence to Decision Factors

- The potential benefits obtained from doing a 1-mg dexamethasone suppression test outweigh the potential harms, as outlined.
- The dexamethasone suppression test requires minimal resources, which include dexamethasone tablets and a blood test for plasma cortisol concentration, and it is widely available worldwide.
- We did not find any published studies on the cost-effectiveness of conducting a 1-mg dexamethasone suppression test. However, it is known to be a relatively cheap and commonly ordered test in endocrinology.
- If the result is abnormal, 2 follow-up tests (24-hour urinary free cortisol and midnight salivary cortisol) are also accessible and inexpensive.
- Furthermore, an understanding of normal adrenal cortisol secretion will reduce confounding in the interpretation of AVS results. Repeating AVS due to uninterpretable results is much more expensive (~$2000-3000 USD) than doing a 1-mg dexamethasone suppression test (~$20) and planning AVS accordingly.
- Individuals rarely decline the dexamethasone suppression test in clinical practice. They may occasionally experience adverse effects from the dexamethasone, but these effects are transient, as the dose of dexamethasone is low and the medication is given only once.

Justification for the Recommendation

The panel based its recommendation on evidence demonstrating that ACS is not uncommon in individuals with PA and can be detected by dexamethasone suppression testing. Having ACS may lead to adverse cardiometabolic consequences, complicate the interpretation of AVS results, and predispose the individual to postoperative adrenal insufficiency following unilateral adrenalectomy. The potential for harm from doing the dexamethasone suppression test is low and relates mainly to unnecessary investigations for Cushing syndrome.

Therefore, the panel concluded that the balance of effects probably favors the intervention and that the test is feasible, accessible, and cost-effective.

Comments

Individuals with adrenally mediated, overt Cushing syndrome and unilateral adrenal adenoma may proceed to surgery, without AVS, to remove the source of excess cortisol.

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Determining the prevalence of mild autonomous cortisol excess, as indicated by an abnormal 1-mg dexamethasone suppression test, in individuals with PA who do not have an adrenal adenoma
- Evaluating the role of adrenal and peripheral vein metanephrine for assessing selectivity and lateralization with the goal of improving guidelines on AVS interpretation in individuals with ACS
- Prospectively evaluating dexamethasone suppression test results and their correlation with AVS and surgical outcomes to establish cortisol cutoffs that guide the need for specific care during AVS (eg, measurement of adrenal vein metanephrine) and the need for perioperative glucocorticoid administration

Medical Treatment for Individuals With Primary Aldosteronism: Spironolactone vs Other Mineralocorticoid Receptor Antagonists

Medical therapy for primary aldosteronism (PA) will likely become the central issue in PA care over the next decade as PA becomes more widely recognized (209). Modern PA series already show that, with expanded PA screening, an increasing majority of PA cases are nonsurgical, bilateral adrenal

hypersecretory states (210). Further, lack of access to AVS necessitates guidance on specific MRA selection.

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:

- 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 (MR) specificity and fewer androgen/progesterone receptor-mediated side effects may be preferred.
- When initiating MRAs, consider hypertension severity for dosing and potential discontinuation of other antihypertensive medications (Fig. 3).
- Monitor potassium, renal function, renin (concentration or activity), and blood pressure (BP) response during follow-up to guide MRA dose titration.

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/FUa-5ocTKo4.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 9 decision making: 1) percent of individuals achieving BP control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) control of hypokalemia, 6) quality of life (QOL), and 7) adverse events.

The systematic review (53) identified 3 relevant randomized controlled trials (RCTs) (122, 211, 212), (n = 229) and 1 comparative observational study (n = 188) with an equal distribution of women and men (29). The meta-analysis concluded that eplerenone, compared with spironolactone, was associated with a higher number of antihypertensive agents and dosage of antihypertensive agents. However, the doses of the medications were not renin-guided to ensure dose-equivalent MR blockade. There were no statistically significant differences in achieving BP control, control of hypokalemia, and SBP level. Data from the direct evidence were insufficient to inform on broad issues of adverse events or QOL, although increased female breast pain and male gynecomastia were reported with spironolactone use. After completion of the systematic review, but prior to publication of these guidelines, 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).

Spironolactone has far greater ability to block androgen action and affect progesterone action than does eplerenone. As this may be relevant to the issue of individual tolerability, the Guideline Development Panel (GDP) considered indirect evidence in the form of studies reporting use other than for a PA indication. Two systematic reviews/meta-analyses were found that compared spironolactone with eplerenone or canrenone (214, 215). One meta-analysis of 14 studies and including 3745 individuals using spironolactone for non-PA indications showed a male gynecomastia incidence rate of 7.9% vs 0.6% among placebo users (OR: 8.39 [5.02-13.99]), although this was still less than that observed in users of anti-androgens or risperidone (214). Among users of MRAs or placebo for heart failure, spironolactone had a relative odds of 8.44 (3.9-18.2) vs eplerenone 0.77 (0.31-1.88) for male gynecomastia (215).

Evidence to Decision Factors

- Studies specifically comparing spironolactone vs other MRAs in medical PA treatment were few in number, small in size, and judged to be low quality. All used surrogate outcomes (eg, BP changes or serum potassium levels), typically ascertained after short treatment intervals. Heterogeneity and unbalanced baseline characteristics in study PA individuals (severe vs mild or mixed PA, lateralizing vs bilateral PA, hypo- or eukalemia) limited the interpretability of meta-analysis. MR-blocking potencies of various MRA agents were not routinely built into treatment protocols, and non-equivalent drug doses were sometimes compared. Dose titration was not uniformly part of the study designs, and, even if so, titration schemes generally did not reflect modern (ie, renin-guided) titration paradigms or BP targets.
- In order to proceed despite the evidence gaps, the GDP agreed to make the following 5 assumptions as part of the EtD process:
  - Each MRA, titrated appropriately, by blocking the MR, likely has an equal chance of eventually achieving the same degree of BP and potassium control in individuals with PA.
  - Each MRA, once titrated to equivalent MR blockade, likely has an equal chance of permitting discontinuation of other antihypertensives.
  - Rates of adverse events may differ between the MRAs.
  - QOL differences may be explained by adverse event rates.
  - QOL differences may exist outside of adverse event occurrences but would need appropriately designed head-to-head comparisons of sufficient duration to detect.
- Expected costs of medical therapy were considered in detail by the GDP, although high-quality cost-effectiveness modeling data in PA specifically is scarce (Table 10).
- It was acknowledged that available studies focused on expected costs would not necessarily translate to all individuals and countries, even among high-resource health systems.
- It was also noted that modeling cost-effectiveness in a PA setting would be highly complex and difficult to perform without high-quality, dose-equivalent MRA comparison studies to rely on.

- Additionally, with PA diagnosed at young or middle ages, a lifetime model must include very long-term costs of therapy balanced against the long-term cost trajectory of reduced disease burden.
- Nonetheless, attempts at cost estimates in other cardiovascular conditions (216-218) consistently demonstrate markedly lower costs for spironolactone vs eplerenone; newer MRA drugs will likely have the highest costs.
- In cost-modeling studies of PA diagnosis and therapy, given the lifelong requirement for MRA treatment in those who do not receive surgery, the cost of medication is expected to rapidly dominate the cost inputs for all but the oldest individuals.
- The GDP made specific note of the individual concerns about tolerability and side effect risk, recognizing the important role of individual preference in choice of MRA, beyond cost considerations alone.

Justification for the Recommendation

Although legitimate individual concerns about tolerability of spironolactone exist, there is no scientific basis in studies of medical efficacy to recommend an alternative MRA as first-line therapy to replace spironolactone. Cost considerations or risk of unwanted anti-androgen effects may be secondary concerns and are likely highly significant when comparing spironolactone vs other MRAs. Shared decision making with individual patients allows for use of a non-spironolactone MRA in PA treatment where desired.

Comments

A recent international consensus document regarding the specific targets and means of implementing optimized MRA therapy has been published (85). As new evidence for new MRAs in PA emerges, recommendations may require updating, although major differential cost considerations may continue to dominate for many years.

Research Considerations

Current gaps in knowledge call for further research in the following areas:

- Evaluating aldosterone synthase inhibitors with appropriately designed PA-specific research studies to determine their optimal position within a PA treatment framework; ongoing trials of MRA drugs such as esaxerenone and aldosterone synthase inhibitors such as dexfadrostat should help clarify relative efficacies in PA therapies both as monotherapy and in combination
- Specifically studying PA with individual-relevant hard clinical endpoints
- Designing and studying more complex treatment paradigms including surgical or procedural-based debulking strategies with and without adjuvant medical therapy

Implementation Considerations

Expanded PA screening in hypertensive individuals is expected to increase diagnosis rates, requiring greater access to additional tests such as adrenal computed tomography (CT) scans and adrenal venous sampling (AVS). These demands may challenge health care systems with limited resources, where access to specialized equipment, expertise, and follow-up care could be uneven. In such settings, pathways involving direct medical treatment, such as initiating MRAs based on screening results alone, may be considered when further testing is not feasible. Variability in resources across settings highlights potential inequities, with rural and low-resource areas facing the greatest barriers. Practical adaptations, such as simplified diagnostic algorithms or regional hubs for specialized care, could mitigate these challenges. Broader implementation will depend on embedding PA screening within existing hypertension management frameworks, supported by education for clinicians and individuals, and ongoing monitoring to ensure benefits reach all populations equitably. To support the adoption of this recommendation and address challenges in implementation, the guideline offers PA screening and management algorithms as practical tools (Figs. 1-3).

Medical Therapy With Epithelial Sodium-Channel Inhibitors vs Mineralocorticoid Receptor Antagonists (Steroidal and Nonsteroidal) for Individuals With Primary Aldosteronism

Background

With increased screening and diagnosis of primary aldosteronism (PA), the need for medical treatment will continue to grow (209). The most commonly used and targeted medical treatments are mineralocorticoid receptor antagonists (MRAs), which are generally widely available and inexpensive. For individuals who cannot tolerate MRAs (eg, due to effects on androgen or progesterone receptors), a lower-cost, second-line option such as epithelial sodium-channel (ENaC) inhibitors may be a consideration.

PA is often associated with resistant or refractory hypertension (219). The significance of aldosterone in resistant hypertension is supported by studies demonstrating that aldosterone synthase inhibitors reduce blood pressure (BP) in treatment-resistant hypertension (220).

In PA, renal sodium reabsorption is increased, leading to volume expansion and higher BP. The increased sodium reabsorption is due to aldosterone-mediated activation of renal mineralocorticoid receptors (MRs) and consequent increased expression and activation of the renal ENaCs (221). Increased ENaC activity leads to increased sodium reabsorption and potassium excretion in the distal convoluted nephron. ENaC is a major regulator of sodium excretion during feedback regulation of BP by the renin–angiotensin–aldosterone system (RAAS) (221, 222).

End-organ damage in individuals with PA is more severe than in individuals with primary hypertension, and includes left ventricular hypertrophy, cardiac fibrosis, arterial stiffness, tubulointerstitial fibrosis, microalbuminuria, and microvascular damage (2, 223, 224). ENaCs are also expressed in the cardiovascular system, and their activation promotes cardiovascular fibrosis, vascular dysfunction, and arterial stiffening (222, 225).

Reducing effects of excess aldosterone by blocking MRs or inhibiting ENaC activation could attenuate PA-induced hypertension, sodium reabsorption, and cardiovascular damage. This suggests the potential utility of ENaC inhibitors like amiloride and triamterene in the treatment of individuals with PA.

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).

Summary of the Evidence

The meta-analysis results, a detailed summary of the evidence and Evidence to Decision (EtD) tables can be found online at https://guidelines.gradepro.org/profile/CssZc_4Ppmg.

Benefits and Harms

The panel voted for the following patient-important outcomes for Question 10 decision making: 1) percent of individuals achieving BP control, 2) number of antihypertensive agents, 3) dosage of antihypertensive agents, 4) systolic BP (SBP) level, 5) adverse cardiovascular events (MACEs), 6) atrial fibrillation, 7) stroke, 8) ischemic heart disease, 9) heart failure, 10) cardiovascular mortality, 11) all-cause mortality, and 12) adverse events.

The systematic review did not find any studies directly comparing ENaC inhibitors vs MRAs in the medical treatment of PA, although a few studies compared ENaC inhibitors and spironolactone (but not eplerenone) in resistant hypertension. Because most individuals with resistant hypertension have PA, we used these studies as indirect evidence of hyperaldosteronism (40, 164).

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). Several smaller studies also demonstrated that amiloride and spironolactone were similarly effective at lowering BP in individuals with resistant hypertension (227-229). In individuals with hypertension and supranormal aldosterone secretion, effects of spironolactone were better than those of amiloride (230). In low-renin hypertension, BP-lowering effects of spironolactone and a hydrochlorothiazide/triamterene combination were similar (231). In volume-dependent hypertension, spironolactone and triamterene reduced BP, with spironolactone having greater effects (232). Together, these studies in resistant hypertension suggest ENaC inhibitors as a viable substitute for spironolactone when spironolactone is not tolerated (233, 234). Beyond similar antihypertensive effects, both amiloride and spironolactone equally improved quality of life (QOL) in individuals with PA (234, 5).

Amiloride may be an effective antihypertensive drug in individuals with PA. However, whether the effects are superior or not to MRAs is unknown because head-to-head trials comparing them in PA are lacking. In a small clinical study in individuals with PA, low-dose amiloride controlled BP within 1 to 4 weeks of initiation, with effects sustained for up to 20 years (227). This was associated with improved vascular function (pulse-wave velocity-indicating cardiac output, vascular resistance, and arterial stiffness) and no cardiovascular events. Amiloride at higher doses corrected hypokalemia and normalized BP in individuals with PA (228).

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.

Evidence to Decision Factors

- Cost-effectiveness data do not exist for ENaC inhibitors in medical PA treatment. However, cost estimates in the United States demonstrated equally low prices for equipotent amiloride and spironolactone.
- Accordingly, amiloride as an alternative to spironolactone may be cost-neutral. (See Question 9 for discussion of cost-effectiveness of spironolactone.)
- Since the clinical impact (BP-lowering) of ENaC inhibitors is the same as spironolactone and given their similar low costs, similar cost-effectiveness is expected from any future model using ENaC inhibition.
- Cost neutrality may be especially relevant in Black individuals who are more likely to have low-renin hypertension (231). Some evidence exists that a significant proportion of these individuals may also have a Liddle-syndrome-type biochemical phenotype, which is strongly responsive to ENaC inhibitors (235).
- Accordingly, inclusion of ENaC inhibitors as an option for low-renin/PA hypertension could increase health equity.

Justification for the Recommendation

Although the evidence is limited and indirect, amiloride seems to be as effective as spironolactone in reducing BP in individuals with resistant hypertension, which the Guideline Development Panel (GDP) used as a surrogate of PA. Both drugs are low cost and both improve QOL. In addition to a lack of direct clinical evidence to recommend the ENaC amiloride over the MRA spironolactone as first-line therapy, questions remain as to whether amiloride would offer all the same benefits as an MRA. There is some justification that MRA should be the preferred treatment in PA based on a small study of 10 individuals with hypertension and supranormal aldosterone secretion in which spironolactone (400 mg/day) had greater BP-lowering effects than did amiloride (40 mg/day) as well as on the clear evidence that MRAs are effective in PA (see Question 9). When spironolactone is not tolerated and other MRAs are not available, amiloride may be an alternative therapy in the management of PA.

Comments and Future Research Considerations

Many gaps in knowledge need to be addressed through robust clinical studies before ENaC inhibitors could be considered a replacement, or add-on therapy, to MRAs, including:

- Comparing ENaC inhibitors vs MRAs in PA
- Studying the potential long-term effects of ENaC inhibitors on end-organ damage in PA, including cardiac, vascular, and renal fibrosis
- Considering diverse populations of PA, including those who are salt-sensitive

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Appendix A. Guideline Development Panel makeup, roles, and management plans

Role	Name	Relevant COI?	Representative
Chair	Gail Adler	No	
Co-Chair	Michael Stowasser	No	
Members	Ricardo Correa	Yes	AACE
	Nadia Khan	No	ISH
	Gregory Kline	No	
	Michael McGowan	No	PAF
	Paolo Mulatero	Yes	ESH
	Rhian Touyz	No	AHA
	Anand Vaidya	Yes	
	Tracy Williams	No	ESE
	Jun Yang	No	
	William Young	Yes	
	Maria Christina Zennaro	No	
Methodologists	M. Hassan Murad	No	
	Juan P. Brito	No	

Abbreviations: AACE, American Association of Clinical Endocrinology; AHA, American Heart Association; COI, conflict of interest; ESE, European Society of Endocrinology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; PAF, Primary Aldosteronism Foundation.

Summary

- Total number of Guideline Development Panel (GDP) members = 13
- Percentage of total GDP members with relevant (or potentially relevant) COI = 31%

Individual Disclosures, Conflicts, and Management Strategies

Chair: Gail K. Adler, MD, PhD
Brigham and Women's Hospital
Expertise: Adult endocrinology

Disclosures (2021-2025):

- National Institutes of Health, Research Funding (various topics)
- Tersus Life Sciences, LLC, Research Funding (insulin sensitivity and lipogenesis)
- American Heart Association, Member of Programming Committee for Hypertension Scientific Conference 2018-2022

- Paris-Cardiovascular Research Center (PARCC) INSERM U970, France, Member of Scientific Advisory Board 2012-2022

Open Payments Database: https://openpaymentsdata.cms.gov/physician/1040596

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Co-Chair: Michael Stowasser, MBBS, FRACP, PhD
University of Queensland
Expertise: Adult endocrinology

Disclosures (2021-2025):
- Springer, Editor-in-Chief for Journal of Human Hypertension

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Ricardo Correa, MD
Cleveland Clinic
Expertise: Adult endocrinology

Disclosures (2022-2025):
- Dynamed
- American Medical Association IMG section
- American Federation of Medical Research
- Association of Program Director of Endocrinology
- Maricopa Medical Association
- ModernaTX, Consulting
- Ascendis Pharma, Speaker
- Neurocrine Biosciences, Consulting
- NovoNordisk, Consulting
- Boehringer Ingelheim (Boehringer Ingelheim manufactures and markets Micardis® (telmisartan), Micardis HCT® (telmisartan and hydrochlorothiazide), and Twynsta® (telmisartan and amlodipine) and is developing vicadrostat, an aldosterone synthetase inhibitor.), Consulting

Pfizer (Pfizer manufactures and markets aldosterone antagonist and Aldactone® (spironolactone) and the anti-hypertensive agents Accupril® (quinapril HCl), Accuretic® (quinapril HCl/hydrochlorothiazide), Norvasc® (amlodipine) and Minipress® (prazosin hydrochloride).), Consulting

Open Payments Database: https://openpaymentsdata.cms.gov/physician/1323034

Assessment and Management:
- Dr. Correa was assessed at the initiation of guideline development of having no industry relationship relevant to the guideline. However, near the end of the development of the guideline, it came to the attention of the Clinical Guidelines Committee Chair that he had 2 consulting entries in Open Payments with 2 companies that had potential relevance to the guideline, Boehringer Ingelheim and Pfizer. Upon assessment of the relationships, the amounts were considered minimal and to not need further mitigation.

Nadia Khan, MD
University of British Columbia
Expertise: Adult hypertension

Disclosures (2023-2025):
- Canadian Institutes for Health Research, co-investigator
- Brain Canada, co-investigator
- Heart and Stroke Foundation of Canada, co-investigator
- International Society of Hypertension, Executive Board Member

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Gregory Kline, MD
Alberta Health Services
Expertise: Adult endocrinology

Disclosures (2023-2025):
- Primary Aldosteronism Foundation, Medical Advisory Board Member

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Michael McGowan
Primary Aldosteronism Foundation
Expertise: Patient representative

Disclosures (2023-2025):
- Cemosoft, consultant
- Brainiest AI Technology, VP and Architect
- Primary Aldosteronism Foundation, various leadership roles

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Paolo Mulatero, MD
University of Torino
Expertise: Adult hypertension

Disclosures (2022-2025):
- Diasorin (Diasorin manufactures and markets Liaison® Hypertension Diagnostic Solution, which includes aldosterone and renin assays.), speaker

Open Payments Database: n/a

Assessment and Management:
- Dr. Mulatero has an industry relationship relevant to this CPG.
- Dr. Mulatero was allowed to participate on the GDP because he is a renowned expert in the area of primary aldosteronism, and since he was nominated by the European Society of Hypertension.
- Divestment: None required.
- COI management: Dr. Mulatero's relationship with Diasorin was deemed potentially relevant to questions related to diagnostic testing. Dr. Mulatero was not involved in systematic reviews for PICO questions directly related to the above considerations. Dr. Mulatero did not vote

on matters directly related to the above considerations. Dr. Mulatero did not draft guideline sections directly related to the above considerations. All GDP participants were made aware of Dr. Mulatero's potentially relevant industry relationship.

Rhian Touyz, MBBCh, MSc, PhD
McGill University
Expertise: Adult hypertension

Disclosures (2022-2025):
- American Heart Association, Editor-in-Chief *Hypertension* journal, Council on Hypertension
- European Society of Cardiology, Co-chair, 2024 ESC guidelines on elevated blood pressure and hypertension

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Anand Vaidya, MD
Brigham and Women's Hospital
Expertise: Adult endocrinology

Disclosures (2021-2025):
- Mineralys Therapeutics (Mineralys Therapeutics is developing lorundrostat, an aldosterone synthase inhibitor.), Advisory Board
- HRA Pharma, Advisory Board
- Corcept, Advisory Board, Consulting

Open Payments Database: n/a

Assessment and Management:
- Dr. Vaidya has an industry relationship relevant to this CPG.
- Dr. Vaidya was allowed to participate on the GDP because he is a renowned expert in the area of primary aldosteronism.
- Divestment: Dr. Vaidya divested from advisory board participation with relevant companies prior to initiation of the guideline.
- COI management: Dr. Vaidya's relationship with Mineralys Therapeutics was deemed potentially relevant to questions related to medical treatment of primary aldosteronism. Dr. Vaidya was not involved in systematic reviews for PICO questions directly related to the above considerations. Dr. Vaidya did not vote on matters directly related to the above considerations. Dr. Vaidya did not draft guideline sections directly related to the above considerations. All GDP participants were made aware of Dr. Vaidya's potentially relevant industry relationship.

Tracy Williams, PhD
Ludwig Maximilian University, Munich
Expertise: Adult endocrinology

Disclosures (2022-2025):
- None

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Jun Yang, MBBS, FRAC, PhD
Hudson Institute of Medical Research
Expertise: Adult endocrinology

Disclosures (2023-2025):
- Primary Aldosteronism Foundation, Patient Engagement Officer
- New Zealand Health and Disability Commission, Expert
- Endocrine Society, Annual Meeting Steering Committee Member
- National Hypertension Taskforce, Member

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

William Young, MD
Mayo Clinic
Expertise: Adult endocrinology

Disclosures (2021-2025):
- Bayer AG (Bayer manufactures and markets the anti-hypertensive agents Pritor ® (telmisartan), Adalt LA® (nifedipine), Baycaron® (mefruside), and Adempas® (riociguat), and the mineralocorticoid receptor antagonist Kerendia® (finerenone).), Consulting, Data Safety Monitoring Board
- AstraZeneca (AstraZeneca manufactures and markets the anti-hypertensive agents Atacand® (candesartan cilexetil), Plendil® (felodipine), and Zestril® (lisinopril) and is developing Baxdrostat, an aldosterone synthetase inhibitor.), Consulting
- Merck Sharp & Dohme (Merck Sharp & Dohme, manufactures and markets the anti-hypertensive Inspra® (eplerenone).), Consulting

Open Payments Database: https://openpaymentsdata.cms.gov/physician/1145085

Assessment and Management:
- Dr. Young has an industry relationship relevant to this CPG.
- Dr. Young was allowed to participate on the GDP because he is a renowned expert in the area of primary aldosteronism.
- Divestment: None required.
- COI management: Dr. Young's relationships with Bayer AG and AstraZeneca were deemed potentially relevant to questions related to medical treatment of primary aldosteronism. Dr. Young was not involved in systematic reviews for PICO questions directly related to the above considerations. Dr. Young did not vote on matters directly related to the above considerations. Dr. Young did not draft guideline sections directly related to the above considerations. All GDP participants were made aware of Dr. Young's potentially relevant industry relationships.

Maria Christina Zennaro, MD, PhD
Université Paris Cité, Inserm, PARCC
Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique
Expertise: Adult endocrinology

Disclosures (2022-2025):
- Springer Nature, Associate Editorial Board, 2022
- French Society of Endocrinology, Leadership
- European Society of Endocrinology, Leadership (completed 2024)
- Endocrine Society, Annual Meeting Steering Committee Member (completed 2022)

Open Payments Database: n/a

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

M. Hassan Murad, MD, MPH
Mayo Clinic
Expertise: Epidemiology, guideline methodology

Disclosures (2021-2025):
- Society for Vascular Surgery, methodologist
- American Society of Hematology, methodologist
- CHEST, methodologist
- World Health Organization, methodologist
- Evidence Foundation, methodologist

Open Payments Database: No entries.

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

Juan P. Brito, MBBS
Mayo Clinic
Expertise: Adult endocrinology, guideline methodology

Disclosures (2021-2025):
- Gordon and Betty Moore Foundation
- National Heart, Lung, and Blood Institute

Open Payments Database: No entries.

Assessment and Management:
- No COI relevant to this CPG.
- No management required.

NOTES ON PRIOR PANEL MEMBERS:

1. An individual with no relevant conflicts of interest was appointed as co-chair at the outset of guideline development but stepped down from the panel in July 2023. This occurred after the development of the PICO questions and prioritization of outcomes, but before the Evidence to Decision process and development of recommendations.

2. An individual with the following relevant relationships was appointed to the panel:
   (a) Daiichi Sankyo (Daiichi Sankyo manufactures and markets the anti-hypertensive agents Olmetec®/Rezaltas®/Sevikar® (Olmesartan medoxomil), Nilemdo® (bempedoic acid) and Nustendi® (bempedoic acid and ezetimibe), and is developing mineralocorticoid receptor inhibitor esaxerenone.): Speaker
   (b) Pfizer manufactures and markets aldosterone antagonist and Aldactone® (spironolactone) and the anti-hypertensive agents Accupril® (quinapril HCl), Accuretic® (quinapril HCl/hydrochlorothiazide), Norvasc® (amlodipine) and Minipress® (prazosin hydrochloride). Speaker

This individual's participation on the panel ended in July 2023, after the development of the PICO questions and prioritization of outcomes, but before the Evidence to Decision process and development of recommendations.

3. An individual with the following relevant relationships was appointed to the panel:
   (a) Mineralys Therapeutics (4Mineralys Therapeutics is developing lorundrostat, an aldosterone synthase inhibitor.): Site Primary Investigator
   (b) Astra Zeneca (AstraZeneca manufactures and markets the anti-hypertensive agents Atacand® (candesartan cilexetil), Plendil® (felodipine), and Zestril® (lisinopril) and is developing Baxdrostat, an aldosterone synthetase inhibitor.): North American Steering Committee Chair

This individual's participation on the panel ended in July 2023, after the development of the PICO questions and prioritization of outcomes, but before the Evidence to Decision process and development of recommendations.

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