The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

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Objective: To develop clinical practice guidelines for the management of patients with primary aldosteronism.

Participants: The Task Force included a chair, selected by the Clinical Guidelines Subcommittee of the Endocrine Society, six additional experts, a methodologist, and a medical writer. The guideline was co-sponsored by American Heart Association, American Association of Endocrine Surgeons, European Society of Endocrinology, European Society of Hypertension, International Association of Endocrine Surgeons, International Society of Endocrinology, International Society of Hypertension, Japan Endocrine Society, and The Japanese Society of Hypertension. The Task Force received no corporate funding or remuneration.

Evidence: We searched for systematic reviews and primary studies to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation group criteria to describe both the quality of evidence and the strength of recommendations. We used "recommend" for strong recommendations and "suggest" for weak recommendations.

Consensus Process: We achieved consensus by collecting the best available evidence and conducting one group meeting, several conference calls, and multiple e-mail communications. With the help of a medical writer, the Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and Council successfully reviewed the drafts prepared by the Task Force. We placed the version approved by the Clinical Guidelines Subcommittee and Clinical Affairs Core Committee on the Endocrine Society's website for comments by members. At each stage of review, the Task Force received written comments and incorporated necessary changes.

Conclusions: For high-risk groups of hypertensive patients and those with hypokalemia, we recommend case detection of primary aldosteronism by determining the aldosterone-renin ratio under standard conditions and recommend that a commonly used confirmatory test should confirm/exclude the condition. We recommend that all patients with primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adrenocortical carcinoma. We recommend that an experienced radiologist should establish/exclude unilateral primary aldosteronism using bilateral adrenal venous sampling, and if confirmed, this should optimally be treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia or those unsuitable for surgery should be treated primarily with a mineralocorticoid receptor antagonist. (*J Clin Endocrinol Metab* 101: 1889–1916, 2016)

Summary of Recommendations

1.0 Case detection

1.1 We recommend case detection of primary aldosteronism (PA) in patients with sustained blood pressure (BP) above 150/100 mm Hg on each of three measurements obtained on different days, with hypertension (BP >140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic), or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years); and all hypertensive first-degree relatives of patients with PA. (1|⊕⊕⊕○○)

1.2 We recommend using the plasma aldosterone/renin ratio (ARR) to detect possible cases of PA in these patient groups. (1|⊕⊕⊕○)

2.0 Case confirmation

2.1 Instead of proceeding directly to subtype classification, we recommend that patients with a positive ARR undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis (1|⊕⊕○○). However, in the setting of spontaneous hypokalemia, plasma renin below detection levels plus plasma aldosterone concentration (PAC) >20 ng/dL (550 pmol/L), we suggest that there may is no need for further confirmatory testing. (2|⊕○○○)

3.0 Subtype classification

3.1 We recommend that all patients with PA undergo adrenal computed tomography (CT) as in the initial study in subtype testing to exclude large masses that may represent adrenocortical carcinoma and to assist the interventional radiologist and surgeon where anatomically appropriate (Figure 1). (1|⊕⊕⊕○)
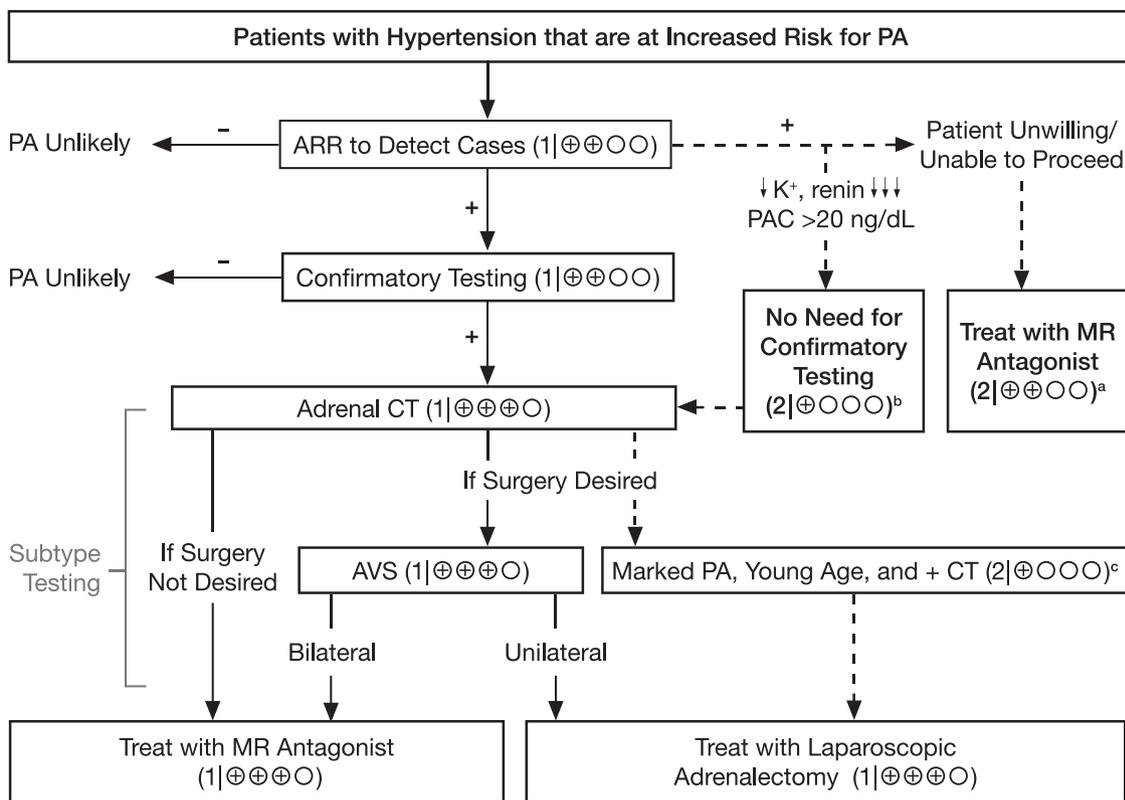

Figure 1. Algorithm for the detection, confirmation, subtype testing, and treatment of PA. [a] We recommend unilateral laparoscopic adrenalectomy for patients with documented unilateral PA (ie, APA or UAH) (1|⊕⊕⊕○). If a patient is unable or unwilling to undergo surgery, we recommend medical treatment including a MR antagonist (1|⊕⊕⊕○). If an ARR-positive patient is unwilling or unable to undergo further investigations, we similarly recommend medical treatment including an MR antagonist (1|⊕⊕○○). [b] Instead of proceeding directly to subtype classification, we recommend that patients with a positive ARR undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis (1|⊕⊕○○). However, in the setting of spontaneous hypokalemia, undetectable renin, and PAC >20 ng/dL (550 pmol/L), we suggest that there may be no need for further confirmatory testing (2|⊕○○○). [c] We recommend that when surgical treatment is feasible and desired by the patient, an experienced radiologist should use AVS to make the distinction between unilateral and bilateral adrenal disease (1|⊕⊕⊕○). Younger patients (<age 35) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy (2|⊕○○○). [Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

3.2 We recommend that when surgical treatment is feasible and desired by the patient, an experienced radiologist should use adrenal venous sampling (AVS) to make the distinction between unilateral and bilateral adrenal disease (1|⊕⊕⊕○). Younger patients (<age 35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy. (2|⊕○○○)

3.3 In patients with an onset of confirmed PA earlier than 20 years of age and in those who have a family history of PA or stroke at a young age (<40 years), we suggest genetic testing for familial hyperaldosteronism type 1 (FH-I) (glucocorticoid remediable aldosteronism [GRA]) (2|⊕⊕○○). In very young patients with PA, we suggest testing for germline mutations in *KCNJ5* causing familial hyperaldosteronism type 3 (FH-III). (2|⊕○○○)

4.0 Treatment

4.1 We recommend unilateral laparoscopic adrenalectomy for patients with documented unilateral PA (ie, aldosterone-producing adenoma [APA] or unilateral adrenal hyperplasia [UAH]) (1|⊕⊕⊕○). If a patient is unable or unwilling to undergo surgery, we recommend medical treatment including a mineralocorticoid receptor (MR) antagonist (1|⊕⊕⊕○). If an ARR-positive patient is unwilling or unable to undergo further investigations, we similarly recommend medical treatment including an MR antagonist. (1|⊕⊕○○)

4.2 In patients with PA due to bilateral adrenal disease, we recommend medical treatment with an MR antagonist (1|⊕⊕○○); we suggest spironolactone as the primary agent, with eplerenone as an alternative (Figure 1). (2|⊕○○○)

4.3 In patients with GRA, we recommend administering the lowest dose of glucocorticoid to lower ACTH and thus normalize BP and potassium levels as the first-line treatment (Figure 1) (1|⊕○○○). In addition, if BP fails to normalize with glucocorticoid alone, an MR antagonist may be added. For children, the glucocorticoid dosage should be adjusted for age and body weight, and BP targets should be determined from age- and gender-specific published normative data.

Foreword

In 2008, the Endocrine Society published clinical guidelines titled *The Case Detection, Diagnosis, and Treatment of Primary Aldosteronism*. Consistent with the Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines (1), the Endocrine Society plans regular updates of its guidelines. Therefore, we incorporated insights from relevant studies over the past 6 years and updated recommendations on PA. Because PA is common and has a much higher cardiovascular risk profile than age-, sex-, and BP-matched essential hypertension, targeted treatment is of obvious benefit to affected patients with hypertension.

For those with confirmed PA, laparoscopic adrenalectomy for unilateral disease cures hyperaldosteronism and hypokalemia and cures or substantially reduces elevated BP. For those with bilateral disease, targeted medical therapy lowers both BP and the deleterious effects of aldosterone hypersecretion. For this reason, we continue to recommend case detection, diagnosis, and treatment of hypertensive patient groups with a relatively high prevalence of PA.

Where the guidelines differ significantly from the previous version is in the explicit recognition of PA as a major public health issue and not merely a matter of case detection, diagnosis, and treatment of individual patients, as might be inferred from the 2008 title.

Because case detection (screening) entails follow-up (confirmation, imaging, AVS, and surgery, if indicated) and these procedures (where available) are expensive, the present rate of screening is very low. Therefore, most subjects with PA are never screened. Our recommendation that a sizeable percentage of those with hypertension undergo screening is thus not a counsel of perfection, but a clarion call to physicians to substantially ramp up the screening of hypertensive patients at risk of PA. As the prevalence of case detection rises, so will demand for the subsequent steps. More PA patients will thus benefit from demand-driven diagnosis and effective treatment.

The question then remains of how to address the major public health issue. Even with modest progress in case detection, diagnosis, and treatment, the overwhelming majority of those with hypertension and occult PA (if and when treated) receive suboptimal care (ie, without targeted MR antagonist therapy). There is no easy solution for this problem, but we need to recognize that the management of PA cannot be confined to those fortunate enough to be screened, diagnosed, and treated.

As physicians, we have a duty to care for all patients suffering from PA, and we should not ignore or gloss over the public health issue that results from patients with PA who go untreated because there are negative consequences for patient and physician.

Method of Development of Evidence-Based Guidelines

In 2006, the Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed detection, diagnosis, and

treatment of patients with PA a priority area in need of practice guidelines and appointed a seven-member Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (2). The recommendations and suggestions made by the Task Force were subject to extensive consultation before being published in the *Journal of Clinical Endocrinology and Metabolism* in 2008 (3). Recently, the CGS of the Endocrine Society concluded that we needed an updated set of practice guidelines, and in 2013 it appointed a second seven-member Task Force, which included members from the earlier group.

Both Task Forces used the best available research evidence to inform the recommendations, and both used consistent language and graphical descriptions of the strength of a recommendation and the quality of the evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that $\oplus$○○○ denotes very low quality evidence; $\oplus\oplus$○○, low quality; $\oplus\oplus\oplus$○, moderate quality; and $\oplus\oplus\oplus\oplus$, high quality. The Task Force has confidence that patients who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the patient's circumstances, values, and preferences to determine the best course of action. A detailed description of this grading scheme has been published elsewhere (4).

Linked to each recommendation is a description of the evidence, the values that panelists considered in making the recommendation (when necessary), and remarks—a section where panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments facilitate the implementation of recommendations and are often derived from the nonsystematic observations of the panelists. One should, therefore, consider them as suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which the Endocrine Society reviews both before and periodically during the development of the guideline to ensure the integrity of Task Force members. Specifically, conflict-of-interest forms are vetted by the CGS before the Society's Council approves the members to participate on the Task Force. Participants in the guideline development must include a majority of individuals without conflicts of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must disclose all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

The Task Force received no funding or remuneration from commercial or other entities because the Endocrine Society provided all support for this guideline.

Systematic reviews

The Task Force identified several existing systematic reviews that addressed various aspects of the diagnosis, treatment, and overall management of PA. We listed these in Table 1, which is titled "Summary of Systematic Reviews Addressing Management of Primary Aldosteronism." The table also provides an explicit description of the outcomes and the quality (certainty) of evidence.

Definition and clinical significance of primary aldosteronism

What is primary aldosteronism?

PA is a group of disorders in which aldosterone production is inappropriately high for sodium status, relatively autonomous of the major regulators of secretion (angiotensin II, plasma potassium concentration), and nonsuppressible by sodium loading. Such inappropriate production of aldosterone causes hypertension, cardiovascular damage, sodium retention, suppression of plasma renin, and increased potassium excretion that (if prolonged and severe) may lead to hypokalemia. PA is commonly caused by an adrenal adenoma, unilateral or bilateral adrenal hyperplasia (BAH), or in rare cases adrenal carcinoma or inherited conditions of familial hyperaldosteronism. PA is also known as Conn's syndrome, in recognition of the researcher who initially described the disorder, its prevalence, and its treatment (9–11).

How common is primary aldosteronism?

Most experts previously described PA in <1% of patients with mild-to-moderate essential hypertension and had assumed that hypokalemia was a sine qua non for diagnosis (12–18). Accumulating evidence has over-

Table 1. Summary of Systematic Reviews Addressing Management of PA

Question	Outcomes	Studies	Certainty in Evidence
Adrenalectomy vs MR antagonists (5)	Adrenalectomy was more effective in reducing BP with no difference in LV mass reduction	Four studies enrolling 355 patients with long-term follow-up (average, 4 y)	BP control (⊕⊕⊕○); no difference in LV mass reduction (⊕⊕○○)
Prevalence of PA (6)	Weighted mean prevalence of elevated ARRs and PA in primary care (prevalence of high ARRs, 16.5%; prevalence of PA, 4.3%) and referred patients (prevalence of high ARRs, 19.6%; prevalence of PA, 9.5%)	11 Observational studies	NA
Accuracy of CT and MRI in diagnosing laterality of aldosterone secretion (adrenal vein sampling is the "gold standard") (7)	Diagnostic accuracy outcome: in 37.8% of patients (359 of 950), CT/MRI results did not agree with AVS results	38 Observational studies (950 patients)	(⊕⊕○○)
Use of ARR as a screening test for PA (8)	Diagnostic accuracy estimates not available (due to methodological limitations)	16 Observational studies (3136 patients)	(⊕○○○)

Abbreviation: NA, not available.

turned these assumptions. Cross-sectional and prospective studies report PA in >5% and possibly >10% of hypertensive patients, both in general and in specialty settings (6, 19–29).

How frequent is hypokalemia in primary aldosteronism?

Only a minority of patients with PA (9 to 37%) has hypokalemia (20, 26). Thus, normokalemic hypertension constitutes the most common presentation of the disease, with hypokalemia probably present in only the more severe cases. In the largest single study to date, half of the patients with an APA and 17% of those with idiopathic hyperaldosteronism (IHA) had serum potassium concentrations <3.5 mmol/L (20). Thus, the presence of hypokalemia has low sensitivity, and the absence of hypokalemia has a low negative predictive value for the diagnosis of PA.

Why is primary aldosteronism important?

This condition is important not only because of its prevalence, but also because patients with PA have higher cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension and the same degree of BP elevation (30, 31). Furthermore, specific treatments are available that ameliorate the impact of this condition on important patient outcomes. Treating PA either by MR antagonists or unilateral adrenalectomy (where indicated) resolves hypokalemia, lowers BP, reduces the number of antihypertensive medications required, and improves parameters of impaired cardiac and renal function. There is continued debate on the noninferiority of medical

treatment for unilateral PA in the longer term, although the current consensus is that unilateral laparoscopic adrenalectomy is the preferred option (32–34).

1.0 Case detection

1.1 We recommend case detection of PA in patients with sustained BP above 150/100 mm Hg on each of three measurements obtained on different days, with hypertension (BP >140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic), or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years); and all hypertensive first-degree relatives of patients with PA. (1|⊕⊕○○)

Evidence

Table 2 summarizes evidence of the increased prevalence of PA in certain patient groups in whom we recommend case detection. There are no clinical trials of screening that measure the impact of this practice on morbidity, mortality, or quality-of-life outcomes. Patients could potentially be harmed by the work-up and treatment (ie, by withdrawal of antihypertensive medication, salt-loading protocols, invasive vascular examination, adrenalectomy) aimed at vascular protection and easier and better BP control. Indirect evidence links the detection of PA with improved patient outcomes. There is strong evidence linking improved BP control and/or reduction in aldosterone lev-

Table 2. Groups With High Prevalence of PA

Patient Group	Prevalence
Moderate/severe hypertension: the prevalence rates cited here are from Mosso et al (27). Others have reported similar estimates (28, 67, 163, 206). We based the classification of BP for adults (aged >18 y) on the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (207), which establishes three different stages: Stage 1 = SBP 140–159 mm Hg, DBP 90–99 mm Hg; Stage 2 = SBP 160–179 mm Hg, DBP 100–109 mm Hg; Stage 3 = SBP >180 mm Hg, DBP = >110 mm Hg (23). When systolic and diastolic BPs were in different categories, the higher category was selected to classify the individual's BP status.	Overall, 6.1%. Stage 1 (mild), 2%. Stage 2 (moderate), 8%. Stage 3 (severe), 13%.
Resistant hypertension, defined as SBP >140 mm Hg and DBP >90 mm Hg despite treatment with three hypertensive medications (56, 193, 208–211).	17–23%
Hypertensive patients with spontaneous or diuretic-induced hypokalemia.	Specific prevalence figures are not available, but more frequently found in this group.
Hypertension with adrenal incidentaloma (141, 212–216), defined as an adrenal mass detected incidentally during imaging performed for extra-adrenal reasons.	Median, 2% (range, 1.1–10%). One retrospective study that excluded patients with hypokalemia and severe hypertension found APA in 16 of 1004 subjects (215).
Hypertension with obstructive sleep apnea (217, 218).	34% among newly hypertensive patients referred to a tertiary referral center and found to have obstructive sleep apnea.

Abbreviations: DBP, diastolic BP; SBP, systolic BP. [Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

els to improved cardiac and cerebrovascular outcomes (33–37) and quality of life (38). Until prospective studies inform us differently, we recommend that all hypertensive first-degree relatives of patients with PA undergo ARR testing.

Values

Our recommendation to detect cases of PA places a high value on avoiding the risks associated with missing a PA diagnosis (and thus forgoing the opportunity of a surgical cure or amelioration of excess cardiovascular morbidity through specific medical treatment); and it places a lower value on avoiding the risk of falsely classifying a hypertensive patient as having PA and exposing him or her to additional diagnostic testing. Our recommendation also places a high value on avoiding the risk associated with missing a diagnosis of unilateral forms of PA and thus the opportunity of possibly curative intervention by unilateral adrenalectomy leading to the reduction or complete cessation of antihypertensive medications (39) and the reduction of target organ damage (32, 36, 40), and it places a lower value on avoiding the risks of exposing patients with bilateral PA (who are rarely candidates for surgical treatment) to additional diagnostic testing.

1.2 We recommend using the plasma ARR to detect possible cases of PA in these patient groups. (1|⊕⊕⊕○)

Evidence

The ARR is currently the most reliable means available for screening for PA. Although valid estimates of test characteristics of the ARR are lacking (mainly due to limitations in the design of studies that have addressed this issue) (8), numerous studies have demonstrated the ARR to be superior in measuring potassium or aldosterone (both of which have lower sensitivity) or renin (which is less specific) in isolation (39, 41, 42). Importantly, laboratories need to report individual values for both PAC and plasma renin activity (PRA)/plasma renin concentration, as well as the ARR.

Like all biochemical case detection tests, the ARR is not without false positives and false negatives (43). Table 3 documents the effect of medications and conditions on the ARR. The ARR should therefore be regarded as a detection test only and should be repeated if the initial results are inconclusive or difficult to interpret due to suboptimal sampling conditions (eg, maintenance of some medications listed in Table 3), or if PA is strongly suspected clinically but the initial screening results are negative.

Values

Similar values underpin our recommendation to target subjects in groups with a documented high prevalence of PA and perform ARR testing. In particular, this recom-

Table 3. Factors That May Lead to False-Positive or False-Negative ARR Results

Factor	Effect on Aldosterone Plasma Levels	Effect on Renin Levels	Effect on ARR
Medications[a]			
β-Adrenergic blockers	D	D D	U (FP)
Central agonists (eg, clonidine, α-methyldopa)	D	D D	U (FP)
NSAIDs	D	D D	U (FP)
K⁺-wasting diuretics	R U	U U	D (FN)
K⁺-sparing diuretics	U	U U	D (FN)
ACE inhibitors	D	U U	D (FN)
ARBs	D	U U	D (FN)
Ca²⁺ blockers (DHPs)	R D	U	D (FN)
Renin inhibitors	D	D U	U (FP)
			D (FN)
Potassium status			
Hypokalemia	D	R U	D (FN)
Potassium loading	U	R D	U
Dietary sodium			
Sodium restriction	U	U U	U (FN)
Sodium loading	D	D D	U (FP)
Advancing age	D	D D	U (FP)
Premenopausal women (vs males)[b]	R U	D	U (FP)
Other conditions			
Renal impairment	R	D	U (FP)
PHA-2	R	D	U (FP)
Pregnancy	U	U U	D (FN)
Renovascular HT	U	U U	D (FN)
Malignant HT	U	U U	D (FN)

Abbreviations: D, down arrow; U, up arrow; R, right arrow; NSAIDs, nonsteroidal anti-inflammatory drugs; K⁺, potassium; ACE, angiotensin-converting enzyme; ARBs, angiotensin II type 1 receptor blockers; DHPs, dihydropyridines; PHA-2, pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate); HT, hypertension; FP, false positive; FN, false negative.

[a] Renin inhibitors lower PRA, but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC.

[b] In premenopausal, ovulating women, plasma aldosterone levels measured during the menses or the proliferative phase of the menstrual cycle are similar to those of men but rise briskly in the luteal phase. Because renin levels are lower, the ARR is higher than in men for all phases of the cycle, but especially during the luteal phase during which aldosterone rises to a greater extent than renin. False positives can occur during the luteal phase, but only if renin is measured as DRC and not PRA. In preliminary studies, some investigations have found false positives on the current cutoffs for women in the luteal phase. Accordingly, it would seem sensible to screen women at risk in the follicular phase, if practicable.

[Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

mendation acknowledges the costs currently associated with ARR testing of all patients with essential hypertension. Against this recommendation for selective testing, however, one must weigh the risk of missing or at least delaying the diagnosis of PA in some hypertensive indi-

viduals. The consequences of this may include the later development of more severe and/or resistant hypertension resulting from failure to lower levels of aldosterone or to block its actions. The duration of hypertension has been reported by several investigators to be a negative predictor of outcome after unilateral adrenalectomy for APA (44, 45), suggesting that delays in diagnosis may result in a poorer response to specific treatment once PA is finally diagnosed.

Remarks: technical aspects required for the correct implementation of recommendation

Testing conditions

The ARR test is most sensitive when samples are collected in the morning after patients have been out of bed for at least 2 hours, usually after they have been seated for 5–15 minutes (Table 4). Ideally, patients should have unrestricted dietary salt intake before testing and should be potassium-replete. In particular, MR antagonists should be withdrawn for at least 4 weeks before ARR testing. In many cases, the ARR can be confidently interpreted despite the effect of continued medications or other suboptimal conditions of testing, thus avoiding delay and/or allowing the patient to proceed directly to confirmatory/exclusion testing. A washout of all interfering antihypertensive medications is feasible in patients with mild hypertension but is potentially problematic in others. The complete cessation of all antihypertensive treatment is usually unnecessary because there are substitute medications that have a minimal effect on the ARR (Table 5). If all potentially problematic agents cannot be safely withdrawn, an ARR should be performed and the results considered in the light of the potential confounding factors. For example, in some patients with severe PA, treatment with an MR antagonist cannot be safely discontinued; in this setting, PA-related testing can be pursued as long as renin is suppressed.

Assay reliability

Clinicians can use an immunometric assay to measure renin either by testing for PRA or for direct renin concentration (DRC); tandem mass spectrometry methodology for measuring PRA has also been developed recently (46). PRA takes into account factors (such as estrogen-containing preparations) that affect endogenous substrate levels. It is preferable that the low-level control material for PRA/DRC comprises a human pool of low-level PRA/DRC samples aliquoted and stored at −80°C that have a PRA value of approximately 0.5 ng/mL/h or a DRC value of approximately 5 ng/L. Because the ARR is mathematically highly dependent on renin (47), renin assays should be sufficiently sensitive to measure levels as low as 0.2–0.3

Table 4.   Measurement of ARR: A Suggested Approach

A. Preparation: agenda
  1. Attempt to correct hypokalemia. Measure plasma potassium in blood collected slowly with a syringe and needle [preferably not a Vacutainer 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. A plasma $[K^+]$ of 4.0 mmol/L is the aim of supplementation.
  2. Encourage patient to liberalize (rather than restrict) sodium intake.
  3. Withdraw agents that markedly affect the ARR (219) for at least 4 weeks:
     a. Spironolactone, eplerenone, amiloride, and triamterene
     b. Potassium-wasting diuretics
     c. Products derived from licorice root (eg, confectionary licorice, chewing tobacco)
  4. If the results of ARR after discontinuation of the above agents are not diagnostic, and if hypertension can be controlled with relatively noninterfering medications (see Table 5), withdraw other medications that may affect the ARR (219) for at least 2 weeks, such as:
     a. β-Adrenergic blockers, central α-2 agonists (eg, clonidine, α-methyldopa), and nonsteroidal anti-inflammatory drugs
     b. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and dihydropyridine calcium channel antagonists
  5. If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR (*e.g.* verapamil slow-release, hydralazine [with verapamil slow-release, to avoid reflex tachycardia], prazosin, doxazosin, terazosin; see Table 5).
  6. Establish OC and HRT status because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured (220). Do not withdraw OC unless confident of alternative effective contraception.
B. Conditions for blood collection
  1. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes.
  2. Collect blood carefully, avoiding stasis and hemolysis (see A.1 above).
  3. Maintain sample at room temperature (and not on ice, as this will promote conversion of inactive to active renin) during delivery to laboratory and prior to centrifugation and rapid freezing of plasma component pending assay.
C. Factors to take into account when interpreting results (see Table 3)
  1. Age: in patients aged >65 years, renin can be lowered more than aldosterone by age alone, leading to raised ARR.
  2. Gender: premenstrual, ovulating females have higher ARR levels than age-matched men, especially during the luteal phase of the menstrual cycle, during which false positives can occur, but only if renin is measured as DRC and not as PRA (220).
  3. Time of day, recent diet, posture, and length of time in that posture
  4. Medications
  5. Method of blood collection, including any difficulty doing so
  6. Level of potassium
  7. Level of creatinine (renal failure can lead to false-positive ARR)

Abbreviations: OC, oral contraceptives; HRT, hormone replacement therapy. [Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

ng/mL/h (DRC, 2 mU/L) (23, 27). Although some laboratories still use RIA for plasma and urinary aldosterone, measured levels of standards have been shown to be unacceptably different in some instances (48). The available RIAs for plasma aldosterone overestimate levels by 50–100% in the range below 200 pmol/L, most probably from cross-reactivity with soluble aldosterone metabolites (49). Published studies have included numerous tandem mass spectrometry methods that have afforded a pathway to assay standardization and improved analytical accuracy (50).

Interpretation

A limitation of the ARR is that in the presence of very low renin levels (for example, at PRA values of 0.1 ng/mL/h), the ARR may be elevated even when plasma aldosterone is also low (for example, 4 ng/dL or 110 pmol/L) and is almost certainly not consistent with PA. To avoid this problem, some investigators include a minimum PAC of >15 ng/dL (410 pmol/L) within the screening criteria (51). However, in one study seated plasma aldosterone levels were <15 ng/dL (<420 pmol/L) in 36% of 74 patients diagnosed with PA who screened positive by ARR and whose aldosterone failed to suppress during the fludrocortisone-suppression test (FST) and in four of 21 patients found by AVS to have unilateral, surgically correctable PA (52); a reasonable inference from this study is that relatively low PAC (that is <15 ng/dL) may be more common in BAH than in patients with APA. Another study reported plasma aldosterone levels of 9–16 ng/dL (250–440 pmol/L) in 16 of 37 patients diagnosed with PA by FST (27). Some investigators therefore proceed with a di-

Table 5. Medications With Minimal Effects on Plasma Aldosterone Levels That Can Control Hypertension During Case Finding and Confirmatory Testing for PA

Drug	Class	Usual Dose	Comments
Verapamil slow-release	Non-dihydropyridine slow-release antagonist calcium channel	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow-release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations)
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two or three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

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agnostic workup for PA in all patients with elevated ARR unless the PAC is below the level used to define normal suppression during confirmatory suppression testing (eg, for the FST, 6 ng/dL or 170 pmol/L) (53). Although a disadvantage of this approach is that the likelihood of a false-positive ARR will be greater, this is counterbalanced by a lower likelihood of missing PA. Of 125 patients who had APAs removed, 20 (16%) had upright midmorning plasma aldosterone levels of <15 ng/dL, and five (4%) had levels <10 ng/dL (280 pmol/L) (43). Therefore, whereas the likelihood of missing APA at levels <10 ng/dL appears to be low, the risk may be greater for PA patients with BAH.

The lack of uniformity in diagnostic protocols and assay methods for measuring the ARR has been associated with substantial variability in cutoff values (24–26, 53–56). Table 6 lists ARR cutoff values using some commonly expressed assay units for PAC, PRA, and the direct measurement of plasma renin concentration.

2.0 Case confirmation

2.1 Instead of proceeding directly to subtype classification, we recommend that patients with a positive ARR undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis (1│⊕⊕○○). However, in the setting of spontaneous hypokalemia, plasma renin below detection levels, plus PAC >20 ng/dL (550 pmol/L), we suggest that there may be no need for further confirmatory testing. (2│⊕○○○)

Evidence

The current literature does not identify a "gold standard" confirmatory test for PA. Most studies evaluated test performance retrospectively in a relatively small series of patients selected with high prior (pretest) probability of

PA and commonly in comparison with other tests, rather than toward a conclusive diagnosis of PA.

Some of these limitations are illustrated in the following example. There is empirical evidence that case-control designs for establishing the accuracy of diagnostic tests overestimate their accuracy. Giacchetti et al (57) used such a design in a study of 61 PA patients (26 with confirmed APA) and 157 patients with essential hypertension. In this context, they found that a postsodium infusion test with a cutoff value for plasma aldosterone of 7 ng/dL (195 pmol/L), when evaluated using receiver operating characteristic

Table 6. ARR Cutoff Values, Depending on Assay and Based on Whether PAC, PRA, and DRC Are Measured in Conventional or Système International (SI) Units

	PRA, ng/mL/h	PRA, pmol/L/min	DRC, mU/L[a]	DRC, ng/L[a]
PAC (as ng/dL)	20	1.6	2.4	3.8
	30[b]	2.5	3.7	5.7
	40	3.1	4.9	7.7
PAC (as pmol/L)	750[b]	60	91	144
	1000	80	122	192

[a] Values shown are on the basis of a conversion factor of PRA (ng/mL/h) to DRC (mU/L) of 8.2. DRC assays are still in evolution, and in a recently introduced and already commonly used automated DRC assay, the conversion factor is 12 (see text). It should be noted that there is poor correlation between DRC and PRA in the range where PRA is <1 ng/mL/h, the domain of major interest in PA screening (221, 222).

[b] The most commonly adopted cutoff values are 30 for PAC and PRA in conventional units (equivalent to 830 when PAC is in SI units) and 750 when PAC is expressed in SI units (equivalent to 27 in conventional units).

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curve analysis, showed a sensitivity of 88% and a specificity of 100% in the 76 cases with ARR >40 ng/dL per ng/mL/h (3.1 pmol/L/min).

In the prospective Primary Aldosteronism Prevalence in Hypertensives study, the analysis of sensitivity/specificity in the 317 patients who underwent a saline infusion test (SIT) gave a best aldosterone cutoff value of 6.8 ng/dL (190 pmol/L). However, the sensitivity and specificity were moderate (83 and 75%, respectively), reflecting values overlapping between patients with and without disease; using the aldosterone-cortisol ratio did not improve the accuracy of the test (58). The same authors reported that the captopril challenge test (CCT) showed similar accuracy when performed under adequate sodium intake conditions (58), although Mulatero et al (59) suggested caution in the interpretation of the CCT because of differences between patients regarding the bioavailability of the drug.

Nanba et al (60) performed a more complex evaluation of three tests (SIT, CCT, and the furosemide upright test [FUT]) in hypertensive patients who tested positive for PA by ARR. The CCT and FUT showed similar levels (~90%) of confirmation/exclusion, whereas the SIT showed lower levels of agreement (<65%) with either the CCT or FUT. Given the similar results of CCT and FUT and the low sensitivity of SIT, the authors proposed that one test (CCT >FUT) should be sufficient to confirm the diagnosis of PA. Finally, Willenberg et al (61) reported divergent results between the SIT and FST and also found a lower cutoff value for SIT than FST; this was in contrast with Mulatero et al (62, 63), who reported a satisfactory agreement between the two tests.

Four testing procedures (oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge) are thus in common use, with the FUT also in use in Japan (64, 65). Despite the reports cited above, definitive evidence that one single test is optimal is lacking, and there is still insufficient direct evidence to recommend one over all the others. Although these tests may differ in terms of sensitivity, specificity, and reliability, the choice of confirmatory test is commonly determined by considering cost, patient compliance, laboratory routine, and local expertise (Table 7).

Clinicians should use caution when administering confirmatory tests requiring oral or iv sodium loading in patients with uncontrolled hypertension or congestive heart failure and should avoid furosemide in subjects at risk of arrhythmia. We recommend that clinicians utilize the pharmacological agents with minimal or no effects on the renin-angiotensin-aldosterone system shown in Table 5 to control BP during confirmatory testing (66). Clinicians should avoid medications known to stimulate renin dur-

ing confirmatory testing because these prevent the suppression of aldosterone (false positive).

In fact, the reproducibility of SITs performed twice after recommended drug withdrawal has been reported to be 84% (66), whereas maintaining established therapy (excluding diuretics and MR antagonists) on one of the two occasions was associated with a reproducibility of only 66% (66). In patients with a baseline PAC >24 ng/dL (670 pmol/L), PAC remained nonsuppressible after the two SITs in both experimental conditions. Nanba et al (60) reported similar data after CCT. These findings support an alternative approach, as already suggested by authors who claim that the diagnosis of PA can be made confidently in patients with a combination of a high ARR and a high level of plasma and urinary aldosterone (51, 67). Given the possible variability in repeat PAC and ARR measurements (68, 69), Letavernier et al (70) consider PA to be present if separate measurements show high recumbent ARR (>63 pmol/mU; 23 ng/mU) plus high PAC (>500 pmol/L; 15 ng/dL) or high upright PAC >550 pmol/L (16.5 ng/dL) or urinary aldosterone levels (>63 nmol/d; 25 μg/d). At the other end of the spectrum, a study reported patients with unilateral hypersecretion at AVS with normal baseline PAC (52); similarly, patients with suppressible aldosteronism on SIT may lateralize on AVS, reflecting the existence of an angiotensin-responsive APA (71).

Finally, researchers have proposed two additional confirmatory tests. The first is the dexamethasone-enhanced FST, whereby roughly 30% of referred hypertensives show PAC values above the range found in normotensive controls (72). In preliminary studies, a seated (as opposed to the usual recumbent) SIT has shown remarkable agreement with the FST, in contrast with much poorer congruence of the recumbent SIT and FST (73). Of 24 patients with confirmed PA, 23 (96%) tested positive by seated SIT compared to only eight (33%) by recumbent SIT (*P* < .001). If larger studies confirm these findings, seated SIT may represent a reliable and more practicable alternative to FST.

Values

Confirmatory testing places a high value on sparing patients with false-positive ARR tests from undergoing costly and intrusive lateralization procedures.

Remarks

For each of the four more common confirmatory tests, we describe procedures, interpretations, and concerns in Table 7.

3.0 Subtype classification

3.1 We recommend that all patients with PA undergo adrenal CT as the initial study in subtype testing to

Table 7. PA Confirmatory Tests

Test and Procedure	Interpretation	Concerns
Oral sodium loading test		
Patients should increase their sodium intake to >200 mmol (~6 g)/d for 3 d, verified by 24-h urine sodium content.	PA is unlikely if urinary aldosterone is <10 μg/24 h (28 nmol/d) in the absence of renal disease where PA may coexist with lower measured urinary aldosterone levels.	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range.	Elevated urinary aldosterone excretion (>12 μg/24 h [>33 nmol/d] at the Mayo Clinic; >14 μg/24 h [39 nmol/d] at the Cleveland Clinic) makes PA highly likely.	24-h urine collection may be inconvenient. Laboratory-specific poor performance of the RIA for urinary aldosterone (aldosterone 18-oxo-glucuronide or acid labile metabolite) may blunt diagnostic accuracy—a problem obviated by the currently available HPLC-tandem mass spectrometry methodology (223).
Urinary aldosterone is measured in the 24-h urine collection from the morning of day 3 to the morning of day 4.		Aldosterone 18-oxo-glucuronide is a renal metabolite, and its excretion may not rise in patients with renal disease.
SIT		
Patients stay in the recumbent position for at least 1 h before and during the infusion of 2 L of 0.9% saline iv over 4 h, starting at 8–9.30 AM. Blood samples for renin, aldosterone, cortisol, and plasma potassium are drawn at time zero and after 4 h, with BP and heart rate monitored throughout the test. In a modified approach, which appears (in preliminary studies) to have much higher sensitivity for diagnosing PA, patients remain in a seated position for at least 30 min and during the infusion (73).	Postinfusion plasma aldosterone levels <5 ng/dL (140 pmol/L) make the diagnosis of PA unlikely, whereas levels >10 ng/dL (280 nmol/L) are a sign of very probable PA. Values between 5 and 10 ng/dL are indeterminate, although a cutoff of 6.8 ng/dL (190 pmol/L) has been found to offer the best trade-off between sensitivity and specificity (57, 58, 224, 225). For the seated SIT, a postinfusion plasma aldosterone of >6 ng/dL (170 pmol/L) confirms PA, provided plasma cortisol concentration is lower than the value obtained basally (to exclude a confounding ACTH effect) (73).	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
FST		
Patients receive 0.1 mg oral fludrocortisone every 6 h for 4 d, together with slow-release KCl supplements (every 6 h at doses sufficient to keep plasma K$^+$, measured four times a day, close to 4.0 mmol/L), slow-release NaCl supplements (30 mmol three times daily with meals) and sufficient dietary salt to maintain a urinary sodium excretion rate of at least 3 mmol/kg body weight. On day 4, plasma aldosterone and PRA are measured at 10 AM with the patient in the seated posture, and plasma cortisol is measured at 7 and 10 AM.	Upright plasma aldosterone >6 ng/dL (170 nmol/L) on day 4 at 10 AM confirms PA, provided PRA is <1 ng/mL/h and plasma cortisol concentration is lower than the value obtained at 7 AM (to exclude a confounding ACTH effect) (39, 52, 53, 112, 226).	Although some centers (23, 27) conduct this test in the outpatient setting (provided that patients are able to attend frequently to monitor their potassium), in other centers several days of hospitalization are customary.
		Most of the data available come from the Brisbane group (39, 52, 53, 89, 112, 226) who have established, on the basis of a very large series of patients, a cutoff of a PAC of 6 ng/dL (170 nmol/L) at 10 AM in an ambulatory patient on day 4.
		Proponents of the FST argue that: a) it is the most sensitive for confirming PA; b) it is a less intrusive method of sodium loading than SIT and therefore less likely to provoke non-renin-dependent alterations of aldosterone levels; c) it allows for the potentially confounding effects of potassium to be controlled, and for ACTH (via cortisol) to be monitored and detected; and d) it is safe when performed by experienced hands.
Captopril challenge test		
Patients receive 25–50 mg of captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldosterone, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period.	Plasma aldosterone is normally suppressed by captopril (>30%). In patients with PA it remains elevated and PRA remains suppressed (58, 60, 163, 227). Differences may be seen between patients with APA and those with IAH, in that some decrease of aldosterone levels is occasionally seen in IAH (228).	There are reports of a substantial number of false-negative or equivocal results (59, 229).

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exclude large masses that may represent adrenocortical carcinoma and to assist the interventional radiologist and surgeon where anatomically appropriate (Figure 1). (1|⊕⊕⊕○)

Evidence

Clinicians use the findings from adrenal CT—normal-appearing adrenals, unilateral macroadenoma (>1 cm), minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macro- or microadenomas (or a combination of the two)—in conjunction with AVS and (if needed) ancillary tests to guide treatment decisions in patients with PA. APA may appear as small hypodense nodules (usually <2 cm in diameter) on CT. Idiopathic adrenal hyperplasia (IAH) adrenal glands may be normal on CT or may show nodular changes. Aldosterone-producing adrenal carcinomas are almost always >4 cm in diameter, but occasionally smaller, and like most adrenocortical carcinomas have a suspicious imaging phenotype on CT (51, 74). Large benign-appearing unilateral masses may represent an aldosterone- and cortisol-secreting adenoma. If this proves to be the case on dexamethasone suppression testing, some centers require AVS, whereas others proceed directly to unilateral adrenalectomy; in either case, patients will require hydrocortisone support postoperatively.

Adrenal CT has several limitations. Radiologists might interpret small APAs incorrectly as "IAH" on the basis of CT findings of bilateral nodularity or normal-appearing adrenals. Moreover, apparent adrenal microadenomas may actually represent areas of hyperplasia or nonfunctioning nodularity, and unilateral adrenalectomy would be inappropriate. In addition, nonfunctioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (>age 35 years) (75), and are indistinguishable from APAs on CT. UAH may be visible on CT, or the UAH adrenal may appear normal on CT.

In one study of 203 patients with PA who were evaluated with both CT and AVS, CT was accurate in only 53% of patients (76). On the basis of CT findings, 42 patients (22%) would have been incorrectly excluded as candidates for adrenalectomy, and 48 (25%) might have had unnecessary or inappropriate surgery (76). In another study, 41 patients had AVS, and the concordance between CT and AVS was only 54% (77). In a systematic review of 38 studies with 950 patients with PA, CT and magnetic resonance imaging (MRI) misdiagnosed the cause of PA in 37.8% of patients (7). Therefore, AVS is essential to direct appropriate therapy in patients with PA who seek a potential surgical cure. CT is particularly useful, however, for detecting larger lesions (eg, >4 cm) that may warrant consideration for removal based on malignant potential

(51, 74). In addition, CT is useful for localizing the right adrenal vein as it enters into the inferior vena cava, thus aiding cannulation of the vein during AVS (78, 79). Finally, the findings on CT may be very helpful in young patients with marked PA (see below).

Remarks

MRI has no advantage over CT in subtype evaluation of PA because it is more expensive and has less spatial resolution than CT.

3.2 We recommend that when surgical treatment is feasible and desired by the patient, an experienced radiologist should use AVS to make the distinction between unilateral and bilateral adrenal disease (1|⊕⊕⊕○). Younger patients (<age 35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy. (2|⊕○○○)

Evidence

Lateralization of the source of the excessive aldosterone secretion is critical to guide the management of PA. Distinguishing between unilateral and bilateral disease is important because unilateral adrenalectomy in all patients with APA or UAH results in the normalization of hypokalemia; hypertension is also improved in all and cured in 30–60% of these patients (32, 44, 80, 81). In bilateral IHA and GRA, unilateral or bilateral adrenalectomy seldom corrects the hypertension (82–86), and medical therapy is the treatment of choice (87). Unilateral disease may be treated medically if the patient declines or is not a candidate for surgery.

Imaging cannot reliably visualize microadenomas or distinguish nonfunctioning incidentalomas from aldosterone-producing adenomas with confidence (76) in most patients, making AVS the most accurate means of differentiating unilateral from bilateral forms of PA. AVS is expensive and invasive, and so it is highly desirable to avoid this test in patients who do not have PA (88). Because ARR testing can be associated with false positives, confirmatory testing should eliminate the potential risk that patients with false-positive ARR undergo AVS.

The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to that of adrenal CT (78 and 75%, respectively) (76, 77, 89). Importantly, CT has the potential to be frankly misleading by demonstrating unilateral adrenal nodules in patients with bilateral disease, and thereby leading to inappropriate surgery.

AVS is the "gold standard" test to distinguish unilateral (APA or UAH) from bilateral (IHA) disease in patients

with PA (76, 89). AVS can be a difficult procedure, especially in terms of successfully cannulating the right adrenal vein (which is smaller than the left and usually empties directly into the inferior vena cava rather than the renal vein); however, the success rate usually improves as the angiographer becomes more experienced. According to a review of 47 reports, the success rate for cannulating the right adrenal vein in 384 patients was 74% (87). With experience, the success rate increases to 90–96% (76, 78, 79, 90, 91). The addition of rapid intra-procedural measurement of adrenal vein cortisol concentrations has facilitated improved accuracy of catheter placement in AVS (92–97). Some centers perform AVS in all patients who have the diagnosis of PA (89, 94). However, in patients younger than 35 years with marked PA (eg, spontaneous hypokalemia; PAC >30 ng/dL, 831 pmol/L) and solitary unilateral apparent adenoma on CT scan, a case can be made to proceed directly to unilateral adrenalectomy without prior AVS (76, 98–101) (Figure 1). In a recent study, of 87 PA patients, a subset of 26 presented with a typical APA on CT and serum potassium <3.5 mmol/L and/or an estimated glomerular filtration rate of at least 100 mL/min/1.73 m^2; all had unilateral PA (100% specificity, 95% confidence interval, 91 to 100; and 53% sensitivity, 95% confidence interval, 38 to 68) (71). However, the utility of these three criteria was not reproducible in two recently published studies (100, 102).

At centers with experienced AVS radiologists, the complication rate is 2.5% or lower (76, 78, 103). The risk of adrenal hemorrhage can be minimized by employing a radiologist skilled in the technique, avoiding adrenal venography, and limiting the use of contrast to the smallest amounts necessary to assess the catheter tip position (79). Where there is a clinical suspicion of a procoagulant disorder, the risk of thromboembolism, which is very low in AVS, may be further reduced by performing tests for such conditions before the procedure and administering heparin after the procedure in patients at risk.

Values

Our recommendation to include AVS in the subtype evaluation of most patients with PA who are candidates for surgery places a high value on avoiding the risk of an unnecessary unilateral adrenalectomy based on adrenal CT and a relatively low value on avoiding the potential complications of AVS.

Remarks

A radiologist experienced with and dedicated to AVS is necessary to implement this recommendation. There are three protocols 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 (104). Many groups advocate the use of continuous cosyntropin infusion during AVS to: 1) minimize stress-induced fluctuations in aldosterone secretion during nonsimultaneous (sequential) AVS; 2) maximize the gradient in cortisol from adrenal vein to inferior vena cava and thus confirm successful sampling of the adrenal vein (105); and 3) maximize the secretion of aldosterone from an APA (76, 84, 90, 106, 107), and thus avoid the risk of sampling during a relatively quiescent phase of aldosterone secretion. Clinicians should avoid administering medications known to stimulate renin in patients undergoing AVS, in that it may lead to the stimulation of the adrenal contralateral to an APA, and unilateral PA might be misclassified as bilateral.

The criteria used to determine the lateralization of aldosterone hypersecretion depend on whether the sampling is done under cosyntropin administration. Dividing the right and left adrenal vein PACs 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 inferior vena cava flow into the right adrenal vein. These are termed "cortisol-corrected aldosterone ratios." With continuous cosyntropin administration, clinicians use a cutoff of the cortisol-corrected aldosterone ratio from high-side to low-side of more than 4:1 to indicate unilateral aldosterone excess (76, 108); a ratio of <3:1 is suggestive of bilateral aldosterone hypersecretion (76). With these cutoffs, AVS for detecting unilateral aldosterone hypersecretion (APA or UAH) has a sensitivity of 95% and specificity of 100% (76). Patients with lateralization ratios between 3:1 and 4:1 may have either unilateral or bilateral disease, and the AVS results must be cautiously interpreted in conjunction with the clinical setting, CT scan, ancillary tests, and if possible, repeat AVS. The contralateral suppression of aldosterone secretion has recently been reported to be helpful in the diagnosis of unilateral PA (109, 110).

Some investigators consider a cortisol-corrected aldosterone lateralization ratio (high to low side) of more than 2:1 in the absence of cosyntropin as consistent with unilateral disease (88, 104, 108). Other groups rely primarily on comparing the adrenal vein aldosterone-cortisol ratios to those in a simultaneously collected peripheral venous sample (89). When the aldosterone-cortisol ratio from an adrenal vein is significantly (usually at least 2.5 times) greater than that of the peripheral vein (cubital fossa or inferior vena cava), and the aldosterone-cortisol ratio in the contralateral adrenal vein is no higher than peripheral

(indicating contralateral suppression), this is interpreted as showing lateralization, an indication that unilateral adrenalectomy should cure or improve the hypertension.

Cosyntropin use

If clinicians do not use cosyntropin infusion, they should perform AVS in the morning hours after overnight recumbency. This approach avoids the confounding effects of changes in posture on aldosterone levels in patients with angiotensin II-responsive varieties of PA and takes advantage of the effect of high early morning endogenous ACTH levels on aldosterone production in all subtypes of PA (79).

If clinicians use cosyntropin infusion, it may be continuous or bolus. For continuous cosyntropin, clinicians should begin an infusion of 50 μg/h of cosyntropin 30 minutes before adrenal vein catheterization and continue it throughout the procedure (76, 84, 90). The bolus cosyntropin technique involves AVS before and after the iv administration of 250 μg of cosyntropin. However, some groups have suggested that when clinicians administer a bolus injection of cosyntropin and sample the adrenal veins simultaneously, cosyntropin does not improve the diagnostic accuracy of AVS, and, in fact, cosyntropin may increase secretion from the nonadenomatous gland to a greater degree than from the APA (20).

Catheterization

Clinicians (commonly interventional radiologists) catheterize the adrenal veins using the percutaneous femoral vein approach and verify the position of the catheter tip by radiography after injecting a small amount of nonionic contrast medium (78, 111). Blood from both adrenal veins and a peripheral vein (labeled peripheral) is taken and assayed for aldosterone and cortisol concentrations. To ensure no cross-contamination, the "peripheral" sample should come from a cubital or iliac vein.

Clinicians typically obtain the venous sample from the left side with the catheter tip at the junction of the inferior phrenic and left adrenal vein. The right adrenal vein may be especially difficult to catheterize because it is short and enters the inferior vena cava at an acute angle (90). Clinicians use the cortisol concentrations from the adrenal veins and peripheral veins to confirm successful catheterization. The adrenal/peripheral vein cortisol ratio is typically more than 5:1 with the continuous cosyntropin infusion protocol (76, 104, 108) and more than 2:1 without cosyntropin use (104, 112).

If both adrenal veins are not successfully catheterized, the decision may be to: 1) repeat AVS; 2) treat the patient medically; or 3) consider surgery based on the findings of other diagnostic tests, as previously noted. A posture stim-ulation test or iodocholesterol scintigraphy may further guide the clinician in this setting.

Posture stimulation test

In patients with unsuccessful AVS and with a CT scan showing a unilateral adrenal mass, some experts use the posture stimulation test. This test, developed in the 1970s, was based on the finding that the PAC in patients with APA showed diurnal variation and was relatively unaffected by changes in angiotensin II levels, whereas IAH was characterized by enhanced sensitivity to a small change in angiotensin II that occurred with standing (113). In a review of 16 published reports, the accuracy of the posture stimulation test was 85% in 246 patients with surgically verified APA (87). The lack of accuracy is explained by the fact that some APAs are sensitive to angiotensin II and some patients with IHA have diurnal variations in aldosterone secretion (114). Thus, the posture stimulation test—particularly if it shows a lack of responsiveness (consistent with angiotensin II-unresponsive APA or hyperaldosteronism type 1 [FH-I], with the latter readily confirmed or excluded by genetic testing)—may serve an ancillary role, for example, in those patients for whom AVS was unsuccessful and CT shows a unilateral adrenal mass (115, 116).

Iodocholesterol scintigraphy

Clinicians first used (131I)-19-iodocholesterol scintigraphy in the early 1970s (117), and an improved agent, (6β-131I) iodomethyl-19-norcholesterol (NP-59), was introduced in 1977 (118). The NP-59 scan, performed with dexamethasone suppression, had the putative advantage of correlating function with anatomical abnormalities. However, the sensitivity of this test depends heavily on the size of the adenoma (119, 120). Because tracer uptake is poor in adenomas smaller than 1.5 cm in diameter, this method often is not helpful in interpreting micronodular findings obtained with high-resolution CT (121) and rarely plays a role in subtype evaluation. Currently iodocholesterol scintigraphy is no longer used in the United States, but it remains in use in Japan and other countries.

18-Hydroxycorticosterone levels

18-Hydroxycorticosterone (18-OHB) is formed by 18-hydroxylation of corticosterone. Patients with APA generally have recumbent plasma 18-OHB levels greater than 100 ng/dL at 8:00 a.m., whereas patients with IAH have levels that are usually less than 100 ng/dL (122). In one study, 18-hydroxycortisol, 18-oxocortisol, and 18-OHB were higher in patients with APA than in patients with IHA or essential hypertension (123). In addition, measuring 18-oxocortisol may have some utility during AVS

(124). More recently, the same group has shown a considerable degree of separation between APA and IHA, with less than 40% of patients not able to be allocated to one or the other on the basis of 18-oxocortisol measurements (125). Until these latter data are reproduced elsewhere, these surrogates and predictors of APA may guide the clinician in selecting patients for AVS but should not be used to direct surgical management (87).

$^{(11)}$C-Metomidate positron emission tomography-computed tomography

Metomidate is a potent inhibitor of adrenal steroidogenic enzymes. A study of 25 patients with PA that used $^{(11)}$C-metomidate—a positron emission tomography radiotracer—reported a specificity of 87% and sensitivity of 76% for APA (126). In the future, APA-specific positron emission tomography radiotracers may have a major role in the subtype evaluation of PA.

3.3 In patients with an onset of confirmed PA earlier than 20 years of age and in those who have a family history of PA or strokes at a young age (<40 years), we suggest genetic testing for FH-I (GRA) (2|⊕⊕○○). In very young patients with PA, we suggest testing for germline mutations in KCNJ5 causing FH-III. (2|⊕○○○)

Evidence

Testing for familial forms of primary aldosteronism: familial hyperaldosteronism type 1 (glucocorticoid remediable aldosteronism)

The FH-I syndrome is inherited in an autosomal dominant fashion and is responsible for 1% of cases of PA (127, 128). The mutation in patients with GRA is fusion of the promoter region of the gene for CYP11B1 and the coding sequences of CYP11B2, resulting in a CYP11B1/CYP11B2 chimeric gene. GRA is a form of hyperaldosteronism in which the hypersecretion of aldosterone is dependent upon endogenous ACTH secretion, which activates aldosterone synthesis. GRA presentation is highly variable, with some patients presenting with normal BP and some characterized by aldosterone excess, suppressed PRA, and hypertension of early onset that is usually severe and refractory to conventional antihypertensive therapies.

Some studies suggest a high pretest probability for GRA in children or young adults with severe or resistant hypertension and a positive family history of early onset hypertension and/or premature hemorrhagic stroke (129, 130). In the study by Dluhy et al (129), 50% of children <18 years of age with GRA had moderate or severe hypertension (BP >99th percentile for age and sex) at diagnosis. Moreover, Litchfield et al (130) reported that in 376 patients from 27 genetically proven GRA pedigrees, 48% of

all GRA pedigrees and 18% of all GRA patients had cerebrovascular complications, with the mean age at the time of the initial event being 32 ± 11.3 years. Seventy percent of events were hemorrhagic strokes with an overall case fatality rate of 61% (130). The study design used in these reports does not allow for the estimation of the yield of new GRA patients that case detection could have permitted in such populations.

Genetic testing by either Southern blot (131) or long PCR (132) techniques for the underlying hybrid CYP11B1/CYP11B2 mutation is sensitive and specific for GRA and should replace indirect testing (eg, urinary levels of 18-oxocortisol and 18-hydroxy-cortisol, or dexamethasone suppression testing), both of which may be misleading (133). Genetic testing for GRA should be considered for PA patients with a family history of PA or of strokes at a young age (130, 134), or with onset at a young age (eg, <20 years).

Testing for familial forms of primary aldosteronism: familial hyperaldosteronism type II

FH-II is an autosomal dominant disorder and possibly genetically heterogeneous (135). Unlike FH-I, the hyperaldosteronism in FH-II does not suppress with dexamethasone, and GRA mutation testing is negative (136). FH-II families may have APA, IAH, or both and are clinically indistinguishable from patients with apparent nonfamilial PA (39). Although FH-II is more common than FH-I, accounting for at least 7% of patients with PA in one series, its true prevalence is unknown (39). In a recent monocentric prospective study of 199 index cases with PA, systematic screening for FH-II in family members resulted in 12 additional families (6%) with 35 affected members (128). The molecular basis for FH-II is unclear, although several linkage analyses have shown an association with chromosomal region 7p22 (135, 137). In a recent European multicenter study of 46 members from 21 families with suspected FH-II (after exclusion of FH-I) (123), one family was found to have a germline mutation in the potassium channel gene KCNJ5 (consistent with a diagnosis of FH-III). Therefore, patients with KCNJ5 mutations may be clinically incorrectly classified as affected by FH-II. Members of two different families had somatic KCNJ5 mutations in APA tissue removed at unilateral adrenalectomy, demonstrating that genetics of FH-II is complex and may involve multiple genetic steps.

Testing for familial forms of primary aldosteronism: familial hyperaldosteronism type III

FH-III was first described in a family characterized by severe hypertension in early childhood associated with hyperaldosteronism, hypokalemia, and resistance to antihy-

pertensive therapy, requiring bilateral adrenalectomy (138). The cause of FH-III is a mutation in the KCNJ5 gene encoding the potassium channel Kir 3.4 (potassium inwardly rectifying channel, subfamily 1, member 5). Mutations occur near the selectivity filter for potassium, resulting in increased sodium conductance and cell depolarization. This opens voltage-activated calcium channels leading to increased calcium signaling, followed by increased aldosterone production and cell proliferation (139). Meanwhile, five more families with FH-III have been described. In one study of four families with FH-III, nine of 10 affected subjects were diagnosed at age 6 or younger, with half undergoing bilateral adrenalectomy for uncontrolled PA (140). In an Italian family, the index case was found to be hypertensive at age 18 and responded well to triple antihypertensive therapy, including low-dose spironolactone, demonstrating that the FH-III phenotype can be mild (123).

Genetic events in sporadic aldosterone-producing adenomas

Starting in 2011, causative somatic mutations in key proteins of adrenal zona glomerulosa cells have been detected in APAs, constitutively altering the function of potassium and calcium channels and ion pumps. Some of the mutations are associated with distinct phenotypic and biochemical characteristics. The detection of the mutational status of the removed adenoma has no current clinical implications for treatment.

KCNJ5 gene

Calcium-dependent signaling is of particular relevance for zona glomerulosa cells to regulate aldosterone secretion. Glomerulosa cell membrane depolarization leads to the opening of voltage-dependent Ca^{2+} channels and the activation of the calcium-signaling pathway. Recently, somatic heterozygous gain-of-function mutations in the KCNJ5 gene have been shown in APAs from PA patients with severe hypertension and hypokalemia (139). The different hot spot mutations identified in APA (p.G151R and p.L168R) and FH-III (p.T158A) are all clustered near or within the selectivity filter of potassium channel Kir3.4 and affect the ion selectivity of the channel, with increased sodium conductance leading to chronic membrane depolarization. These changes are responsible for increased calcium influx into the cell, leading to constitutive secretion of aldosterone and possibly cell proliferation (35, 141). Since its first publication, large collections of sporadic APAs have been screened worldwide, demonstrating that KCNJ5 mutations are present in 10 to 68% of APAs (142–145). Patients with KCNJ5 mutations are younger on presentation, and more often female than male.

ATP1A1 and ATP2B3

Recently, researchers have described recurrent somatic mutations in two new genes, ATP1A1, coding for the α-subunit of the Na^+/K^+-ATPase, and ATP2B3, coding for the plasma membrane calcium-transporting ATPase 3 (PMCA3) (146). The mutations occurred in highly conserved regions involved in interaction with the transported cation, potassium for Na^+/K^+-ATPase and calcium for PMCA3. In vitro studies have shown that the ATP1A1 mutations significantly reduced Na^+/K^+-pump activity, as well as the apparent affinity of Na^+/K^+-ATPase for K^+. Somatic ATP1A1 mutations were present in 5.2% and ATP2B3 mutations in 1.6% of patients. Patients carrying these somatic adrenal mutations commonly show increased plasma aldosterone and lower potassium than noncarriers, similar to patients with somatic KCNJ5 mutations. However, in contrast with patients with somatic KCNJ5 mutations, ATPase mutations are more common in males (146).

CACNA1D gene

Two jointly published studies from the United States and the United Kingdom reported somatic mutations in a gene (CACNA1D) encoding a voltage-gated calcium channel (147, 148). The mutations were found in 11 and 5% zona glomerulosa-like APAs without KCNJ5 mutations. The CACNA1D mutations affect conserved sites within functional domains of the Cav1.3 channels responsible for the channel activation gate. This increases intracellular Ca^{2+} entry leading to Ca^{2+}-mediated signaling and enhanced aldosterone secretion. In addition, Scholl et al (147) reported de novo (ie, not inherited) but germline mutations in CACNA1D in two children with a previously undescribed syndrome featuring PA and neuromuscular abnormalities.

Multiple endocrine neoplasia type 1

Finally, APA may rarely but on occasion be seen in multiple endocrine neoplasia type 1.

4. Treatment

Cardiovascular complications

Hypertension is the rule in patients diagnosed with PA and is cured or improved by unilateral adrenalectomy in patients with unilateral disease and improved by MR antagonists in the remaining patients. In addition, aldosterone excess has deleterious effects on the cardiovascular system, at least partly independent of its effects on BP. The pathophysiology was first established in animal models and subsequently was clearly demonstrated by several studies on PA patients (149). Such studies showed increased left ventricular (LV) dimensions and myocardial

fibrosis (150–152), increased carotid intima-media thickness (153, 154), and increased femoral pulse wave velocity and reduced endothelial function (155).

Several outcome studies also have provided evidence that PA patients are particularly at risk of cardiovascular/renal complications, including arrhythmias, myocardial infarction, strokes, chronic kidney disease, and death, compared with age-, sex-, and BP-matched essential hypertensives (30, 33, 156). It is therefore not sufficient merely to control hypertension in patients with PA because increased LV wall thickness and reduced diastolic function have been shown in normotensive patients with FH-I (31).

The Framingham Offspring Study suggested the involvement of aldosterone in the development of arterial hypertension in the general population, in which plasma aldosterone levels in normotensive subjects predicted subsequent increases in BP and the development of hypertension (157). This observation suggests that PA and MR overactivation play a crucial role in not only cardiovascular complications but also a risk of developing hypertension. Recent reports from the German Conn's registry showed cardiovascular mortality to be the main cause of death in PA; however, these reports also showed that whereas cardiovascular mortality is increased in patients treated for PA, all-cause mortality is not different from matched hypertensive controls (33).

Either unilateral adrenalectomy or MR antagonist therapy can reverse the cardiovascular morbidity caused by aldosterone excess (158). Researchers reported that arterial stiffness (measured as carotid-femoral pulse wave velocity and augmentation index) was reduced by unilateral adrenalectomy but not after 1 year of spironolactone treatment in PA (159). Catena et al (36) showed surgery to be more effective than spironolactone treatment in reducing LV mass after 1 year, but overall reduction from baseline was comparable by the end of the study (mean follow-up, 6.4 years). A recent nationwide survey in Japan showed that surgical therapy improved both hypertension and hypokalemia more than medical therapy in unilateral and/or bilateral aldosterone-producing adenomas; one possible caveat is that eplerenone was not used in the survey (160). Overall, these data provide compelling support for early detection of individuals with PA who can then benefit from improved cardiovascular outcomes affected by specific surgical or medical treatment.

4.1 We recommend unilateral laparoscopic adrenalectomy for patients with documented unilateral PA (ie, APA or UAH) (1|⊕⊕⊕○). If a patient is unable or unwilling to undergo surgery, we recommend medical treatment including a MR antagonist (1|⊕⊕⊕○). If an ARR-positive patient is unwilling or unable to undergo further investi-

gations, we similarly recommend medical treatment including an MR antagonist. (1|⊕⊕○○)

Evidence

Clinicians use unilateral laparoscopic adrenalectomy in patients with unilateral PA because BP and serum potassium concentrations improve in nearly 100% of patients postoperatively (80, 161–165). Hypertension is cured (defined as BP <140/90 mm Hg without the aid of antihypertensive drugs) in about 50% (range, 35–80%) of patients with APA after unilateral adrenalectomy (32, 38, 81, 161), with a "cure" rate as high as 56–77% when the cure threshold is BP <160/95 mm Hg (44, 166, 167), which is clearly still in the hypertensive range. There is little high-quality evidence linking adrenalectomy with improved quality of life, morbidity, or mortality. Recently, however, a large case-control study demonstrated a similar mortality of patients with PA treated with either adrenalectomy or MR antagonists compared with mortality of patients with essential (primary) hypertension (33). In addition, adrenalectomy induces a significant and sustained reduction in LV mass index due to a reduction in LV diameter and volume with a reduction in LV workload (improvement in diastolic dysfunction) (32). Adrenalectomy also appears to reverse the increase in carotid intima-media thickness and arterial stiffness in patients with unilateral PA (34). Two prospective studies also reported the reversal of albuminuria 1 year after adrenalectomy (40, 168), and another study reported significant improvement in quality of life by 3 months sustained at 6 months (38).

Factors associated with hypertension resolution in the postoperative period include having one or no first-degree relative with hypertension and preoperative use of two or fewer antihypertensive drugs (80). Other factors that have been reported to predict cure, but have only been evaluated by univariate analysis or when the cutoff for BP resolution was <160/95 mm Hg (44, 161), include: duration of hypertension <5 years (44, 45, 80, 81), higher PAC:PRA ratio preoperatively (80, 81), higher urinary aldosterone secretion (80, 81), or positive preoperative response to spironolactone (81, 162). The most common reasons for persistently increased BP after adrenalectomy are coexistent primary hypertension (of unknown cause) (44, 80) and older age and/or longer duration of hypertension.

Compared with open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications (163, 169, 170). Because AVS is able to identify only which gland (and not which part of the gland) is overproducing aldosterone, partial adrenalectomy (removal of an adenoma leaving the remaining

adrenal intact) may result in persistent hypertension. Continued PAC elevation is found in up to 10% of patients with unilateral APA, and 27% of extirpated adrenal glands are found to contain multiple nodules (171).

Medical management is recommended for patients who do not undergo surgery. In a retrospective study of 24 patients with APA who were treated for 5 years with spironolactone or amiloride, systolic and diastolic BP decreased from an average of 175/106 to 129/79 mm Hg (172), with 83% of these patients requiring additional antihypertensive medication to achieve this result. Side effects of spironolactone are dose-dependent and include gynecomastia, breast engorgement, erectile dysfunction, and muscle cramps. In the long-term, adrenalectomy is more cost-effective than lifelong medical therapy for patients with unilateral PA (173, 174).

Therefore, because unilateral laparoscopic adrenalectomy can either eliminate the need for medication or reduce medication-related side effects, it is the preferred procedure for the treatment of unilateral disease in patients with PA.

Values

Our recommendation that laparoscopic adrenalectomy is preferable to other methods of treatment in patients with unilateral adrenal disease places a high value on the normalization of endogenous aldosterone secretion, the resolution of hypokalemia, and the reduction of BP and/or the number of medications necessary to control BP. This benefit is far greater than the risks of surgery and postoperative management, which are very low.

Remarks

This recommendation requires the availability of a surgeon experienced in laparoscopic adrenalectomy.

Preoperative management

Both hypertension and hypokalemia should be well controlled before patients undergo surgery. Obtaining such control may require a delay in surgery and the addition of an MR antagonist.

Postoperative management

Clinicians should measure plasma aldosterone and renin activity levels shortly after surgery as an early indication of biochemical response (165), although renin levels may not fall immediately. They should also withdraw potassium supplementation on postoperative day 1, discontinue spironolactone, and reduce antihypertensive therapy, if appropriate (175).

Postoperative iv fluids should be normal saline without potassium chloride unless serum potassium levels remain very low (ie, <3.0 mmol/L); during the first few weeks after surgery, clinicians should recommend a generous sodium diet to avoid the hyperkalemia that can develop from hypoaldosteronism due to chronic contralateral adrenal gland suppression (175, 176). Persistent hypoaldosteronism requiring mineralocorticoid replacement therapy (fludrocortisone) may occur in up to 5% of adrenalectomized patients (176). Preoperative reduced glomerular filtration rate and increased serum creatinine as well as postoperative increased creatinine and microalbuminuria are significant predictors of postoperative hyperkalemia (176).

BP typically normalizes or shows maximum improvement in 1–6 months after unilateral adrenalectomy for unilateral APA but can continue to fall for up to 1 year in some patients. Some investigators have employed postoperative FST (performed at least 3 months after surgery to permit recovery of the contralateral gland) to assess whether the PA has been cured from a biochemical perspective (177). Seated SIT, which appears in preliminary analysis to be much more sensitive than recumbent SIT for diagnosing PA (73), holds promise as a more practical alternative to FST in this regard, but has yet to undergo formal evaluation in the postoperative setting.

4.2 In patients with PA due to bilateral adrenal disease, we recommend medical treatment with an MR antagonist (1|⊕⊕○○); we suggest spironolactone as the primary agent, with eplerenone as an alternative (Figure 1). (2|⊕○○○)

Evidence

Bilateral adrenal disease includes IAH, bilateral APA, and GRA. In 99 surgically treated patients with IAH reported in the literature, the hypertension cure rate was only 19% after unilateral or bilateral adrenalectomy (82–86). A randomized controlled trial has demonstrated that spironolactone may be more effective than eplerenone in controlling BP in patients with PA, albeit the doses of spironolactone were higher than commonly employed and eplerenone was only given once daily (178). In a smaller study, eplerenone and spironolactone were in contrast found to be equipotent in reducing BP in patients with confirmed PA (179). However, the pathophysiology of PA due to BAH and long-standing clinical experience suggest several pharmacological targets.

MR antagonists

MR antagonists appear to be effective at controlling BP and protecting target organs independent of effects on BP.

Spironolactone

For more than five decades, the MR antagonist spironolactone has been the agent of choice in the medical treatment of PA. Several observational studies in patients with IAH (combined n = 122) have reported mean reductions in systolic BP of 25% and diastolic BP of 22% in response to spironolactone 50–400 mg/d for 1–96 months (180–186). In a study of 28 hypertensive subjects with an ARR >750 pmol/L (27 ng/dL)/ng/mL/h who failed to suppress their PAC after salt loading and had no evidence of adenoma on adrenal CT scan, spironolactone therapy (25–50 mg/d) reduced the need for antihypertensive drugs by 0.5 drugs (from a mean of 2.3 to 1.8 drugs) and reduced systolic BP by 15 mm Hg (from a mean of 161 to 146 mm Hg) and diastolic BP by 8 mm Hg (from a mean of 91 to 83 mm Hg); 48% of subjects achieved a BP <140/90 mm Hg, and about half were able to be managed with spironolactone monotherapy (187). The dose of spironolactone the study employed was much lower than previously considered necessary for the treatment of PA.

The incidence of gynecomastia with spironolactone therapy is dose-related, with one study reporting an incidence after 6 months of 6.9% at a dose <50 mg/d and 52% at a dose >150 mg/d (188). The exact incidence of menstrual disturbances in premenopausal women with spironolactone therapy is unknown. Where available, canrenone (an active metabolite of spironolactone) or potassium canrenoate (its open E-ring water soluble congener) might be considered. In addition, a small dose of a thiazide diuretic, triamterene, or amiloride can be added to attempt to avoid a higher dose of spironolactone, which may cause side effects.

Eplerenone

Eplerenone is a newer, selective MR antagonist without antiandrogen and progesterone agonist effects (189), thus reducing the rate of adverse endocrine side effects. It has been approved for the treatment of primary (essential) hypertension (190, 191) in the United States and Japan, and for heart failure after myocardial infarction (192) in the United States and a number of other countries. Eplerenone in vivo has 50% of the MR antagonist potency of spironolactone. Its better tolerability profile needs to be balanced against its higher cost and the possibility that spironolactone may lower BP more effectively than eplerenone in the medical treatment of PA (178). Reflecting its shorter half-life, eplerenone should be given twice daily for optimal effect.

Other agents

The up-regulation of distal tubular sodium epithelial channel activity is a major mechanism whereby aldoste-rone exerts its actions on sodium and potassium handling. Of the two available epithelial sodium channel antagonists amiloride and triamterene, amiloride has been the more studied as a mode of treatment for PA. Although less efficacious than spironolactone (193, 194), amiloride does have some advantages. Being a potassium-sparing diuretic, amiloride can ameliorate both hypertension and hypokalemia in patients with PA and is generally well tolerated. It lacks the sex steroid-related side effects of spironolactone but does not provide the beneficial effects on endothelial function (195, 196).

Calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have been evaluated in very few patients with PA, and in general they are antihypertensive without a major effect on MR activation. They are, nevertheless, commonly used to lower BP (in combination with MR antagonists) if BP remains above normal. Aldosterone synthase inhibitors may play a role in the future.

Values

This recommendation places a relatively higher value on normalizing serum potassium concentrations; reducing BP; and eliminating the vascular, cardiac, and renal effects of aldosterone with the minimum number of pharmacological agents, and a relatively lower value on side effects such as gynecomastia and erectile dysfunction in men and menstrual irregularities in women. Eplerenone, given its selectivity and despite its cost, is an alternative if the side effects of spironolactone prove difficult to tolerate.

Remarks

The starting dose for spironolactone should be 12.5 to 25 mg/d in a single dose. The lowest effective dose should be found by very gradually titrating upward, if necessary, to a maximum dose of 100 mg/d. The starting dose for eplerenone is 25 mg twice daily. In patients with stage III chronic kidney disease (ie, glomerular filtration rate <60 mL/min/1.73 m^2), clinicians should administer spironolactone and eplerenone with caution because of the risk of hyperkalemia; clinicians should avoid administering MR antagonists in patients with stage IV disease.

Observations suggest that patients with PA may have reversible reduction in intrarenal vascular resistance and glomerular hyperfiltration, which may disguise the underlying renal injury, including declining glomerular filtration rate and albuminuria (40, 197). Treating PA by adrenalectomy or with an MR antagonist frequently unmasks the underlying reduction in renal function in patients with PA (198, 199).

4.3 In patients with GRA, we recommend administering the lowest dose of glucocorticoid to lower ACTH and

thus normalize BP and potassium levels as first-line treatment (Figure 1) (1│⊕○○○). In addition, if BP fails to normalize with glucocorticoid alone, an MR antagonist may be added. For children, glucocorticoid dosage should be adjusted for age and body weight, and BP targets should be determined from age- and gender-specific published normative data.

Evidence

GRA should be treated medically with a glucocorticoid to partially suppress pituitary ACTH secretion. We recommend administering a synthetic glucocorticoid that is longer acting than hydrocortisone, such as dexamethasone or prednisone, to suppress ACTH secretion. Ideally, the glucocorticoid should be taken at bedtime to suppress the early morning ACTH surge. Plasma renin activity and aldosterone concentrations may be helpful in assessing the effectiveness of treatment and the prevention of overtreatment.

Overtreatment with exogenous steroids must be avoided; iatrogenic Cushing's syndrome and impaired linear growth in children have resulted from such overdosing (129). In general, clinicians should use the lowest possible dose of glucocorticoid that normalizes BP and/or serum potassium concentration (79). Treating with a glucocorticoid may not always normalize BP, and clinicians should consider adding an MR antagonist in these cases. Treatment targets for BP in children should be determined from published age- and gender-specific normative data (200, 201). Glucocorticoid doses in children vary by age and body weight (128).

The use of eplerenone may be preferred in the case of affected children, in whom there may be concerns with respect to growth retardation and the antiandrogenic effects of glucocorticoids and spironolactone, respectively.

Values

The treatment of GRA places a high value on preventing the potential consequences of hyperaldosteronism and a lower value on the possible side effects of chronic glucocorticoid administration.

Remarks

The starting dose of dexamethasone in adults is 0.125–0.25 mg/d. The starting dose of prednisone is 2.5–5 mg/d. For each, treatment is usually administered at bedtime.

Perspectives

The revised guidelines make recommendations and suggestions for the management of PA on the evidence, both scientific and societal. Over the next 5 years, management should have further evolved; as a guide to where

progress might (and should) be made, we offer the following commentary.

There are currently on the market only two classes of MR agonists (MRAs). Spironolactone and its congeners canrenone and potassium canrenoate are generation 1, with high MR affinity but major side effects due to nonselectivity. Eplerenone is the generation 2 MRA, with low MR affinity, but it is selective (and expensive); both have an obligate effect of an elevation in plasma potassium in subjects without PA, thus limiting their use. In many countries, eplerenone is not approved for hypertension (including PA); in some countries even spironolactone is not easily reimbursable for hypertension. The side effects of spironolactone are well known and an issue in terms of compliance; eplerenone is more expensive than spironolactone. Diabetes is not a contraindication to the use of eplerenone, despite the package insert, providing patients are carefully monitored in terms of plasma (K$^+$) and renal function.

In the next 5 years, it is likely that generation 3 MRAs (nonsteroidal, as potent as spironolactone, and as selective as eplerenone) and perhaps selective aldosterone synthase inhibitors will be available for the treatment of PA. For additional uses of MRAs (eg, heart failure, fibrotic disorders), generation 4 MRAs may also be available (nonsteroidal, potent, selective, and tubule sparing to lessen the extent of elevating plasma potassium).

Over the same period, there will need to be a number of advances within the medical centers where clinicians refer patients with possible PA. At present, we have only estimates of the annual numbers of patients diagnosed and treated (medically or surgically) for PA. We need registries (such as those that exist in Germany) on a regional and/or national basis; in conjunction with these registries, there should also be blood and tissue biobanks.

We urgently need the revision of an agreement on normal ranges for PAC, DRC, and PRA, with standardized and quality-controlled assays. If the normal range for PAC is 3–31 ng/dL in Ancona, Italy, and 4–21 ng/dL in Rochester, Minnesota, we have not only a 2-fold difference in range for what is considered normal, but also a strong indication that such a 5- to 10-fold variation in "normal" PAC may reflect not only differences in sodium intake but also variations in sensitivity to aldosterone (as have been shown between African Americans and those of Caucasian ancestry) (202).

Over the next 5 years, we may settle upon on a rapid, inexpensive, and safe confirmatory/exclusion test for patients with possible PA on screening. In preliminary studies, a seated SIT proved far superior to the conventional recumbent SIT, and equivalent to the FST. The possibility that inclusion of overnight dexamethasone would uncover an additional approximately 20% of hypertensives with

inappropriate aldosterone secretion, as found in the dexamethasone-enhanced FST, represents a major possible advance.

Many practicing physicians were taught that PA is a rare and benign cause of hypertension, and in terms of diagnosis and treatment thus merely a footnote to the management of hypertension as a whole. Cardiologists usually write guidelines for hypertension with some input from nephrologists and clinical pharmacologists and little or none from endocrinologists; the recent European Society of Hypertension Guidelines (203) nicely illustrate this point.

In the next 5 years, cardiologists and endocrinologists need to work together so that those whose responsibility is primary care are made keenly aware that the prevalence of PA, as currently defined, is roughly 10% in hypertensives, and that it is even higher in certain groups (hypokalemia, higher BP, resistant hypertension), with another roughly 20% having "inappropriate aldosterone secretion" and responding specifically to MRAs.

Nationally (204) and internationally (205), hypertension is recognized as the most significant risk factor for death and disability. Within hypertension, 5% of patients have florid PA, predominantly APA, and another 5% have clear but less florid PA, primarily IAH. As noted above, in an additional approximately 20% of patients (resistant hypertension, low renin hypertension), MRAs are remarkably effective in lowering BP. It is also established that within hypertension, patients with PA have a much higher risk of atrial fibrillation, nonfatal myocardial infarct, and stroke than age-, sex-, and BP-matched essential hypertensives; in some centers patients presenting with atrial fibrillation have both TSH and ARR measured. All of these factors taken together clearly indicate that PA is a major public health issue requiring urgent attention and concerted action.

Refinements in the diagnosis and treatment of PA, some of which are listed above, are almost certain to emerge over the next 5 years; the main strategy is to convince primary care physicians to screen for PA in all at-risk hypertensive patients. To this end, three things (at least) are desirable, and the first immediately practicable.

First, in parallel with these guidelines (which are targeted at endocrinologists and other specialists involved in the diagnosis and treatment of PA), we are developing a simple and accessible guideline for screening and referral for widespread national and, if possible, international distribution.

Secondly, and very urgently, the development of methods to measure PAC and DRC in the same sample, as an aid to screening in primary care, are currently in develop-

ment. Optimally, a point-of-care test to accurately measure PAC and DRC—analogous to the currently available strips for plasma glucose, D-dimer, etc—would be a game-changer for the primary care physician. Whether or not the current strict regime of drug withdrawal is totally necessary is an area of conjecture and debate; if the test is inexpensive enough, it may be that only MRAs absolutely need to be withdrawn before screening.

Finally, and debatably, it may be appropriate that at-risk patients who do not undergo screening routinely have a low-dose MRA included in their antihypertensive regimen.

5.0 What is new?

The revised 2015 guidelines for the management of PA build on and extend the 2008 guidelines in a number of areas, as follows:

- Broadened indications for screening, to include subjects with sustained BP elevation above 150 mm Hg (systolic) and/or 100 mm Hg (diastolic).
- Recognition that stringent cutoffs for ARR and PAC produce a positive rate of approximately 5% of hypertensives with PA as so defined, most of whom have a unilateral APA; less stringent cutoffs give a positive rate of 10%, with the majority having IAH as the source of autonomous aldosterone secretion.
- Details of recent findings establishing somatic mutations as (currently) the explanation of aldosterone hypersecretion in approximately 50% of APA, and of similar germline mutations in FH-III.
- Strengthening the case for timely diagnosis and treatment of PA, based on mounting evidence for cardiovascular and renal damage.
- Explicit recommendations for referral by primary care physicians of patients with suspected PA to specialized centers for further work-up.
- Explicit suggestions for an abbreviated work-up in patients with spontaneous hypokalemia, renin levels below the detection limit plus florid hyperaldosteronism.
- Enhanced communication among and between care providers to optimize outcomes for patients with confirmed PA.
- Recognition that capacity constraints mean that most patients with PA will be unable to be screened in the foreseeable future, and that given the heightened risk profile of PA and its frequency in hypertension, occult PA constitutes a major public health issue.

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