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Clinical Practice Guideline Systematic Review

A Systematic Review Supporting the Endocrine Society Clinical Practice Guideline on Management of Primary Aldosteronism

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Abstract

Context: Primary aldosteronism (PA) is a leading endocrine cause of secondary hypertension.

Objective: To support the development of the Endocrine Society Clinical Practice Guideline on managing PA.

Data Source: MEDLINE, Embase, Scopus, and others were searched on October 4, 2024.

Study Selection: Studies were selected by pairs of independent reviewers.

Data Extraction: Data were extracted and appraised by pairs of independent reviewers.

Data Synthesis: We included 95 studies (7 randomized trials and 88 observational studies). We did not identify trials that evaluated the outcomes of PA screening. One observational study suggested that screening was associated with higher rates of using PA-specific medical therapies and better blood pressure control. Patients managed with adrenal venous sampling (vs computed tomography alone) may have a better post-adrenalectomy biochemical cure rate, but with an increased risk of adrenal hemorrhage. Two small observational studies suggested that PA-specific medical or surgical therapy was likely associated with better blood pressure control than nonspecific therapy. Small randomized trials suggested that surgical therapy may be associated with better blood pressure control than medical therapy, with a lower number and dosage of antihypertensive medications. Compared to eplerenone, spironolactone may be associated with better control of hypokalemia and a lower number and dosage of antihypertensive agents. Unsuppressed plasma renin activity was associated with better control of hypokalemia, while suppression was associated with higher risk of mortality, atrial fibrillation, and stroke (very low certainty).

Conclusion: This systematic review addresses various aspects of managing PA and will support the development of the Endocrine Society guidelines.

Key Words: primary aldosteronism, Endocrine Society, guidelines, systematic review, meta-analysis

Abbreviations: AVS, adrenal venous sampling; CT, computed tomography; eGFR, estimated glomerular filtration rate; MD, mean difference; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; PA, primary aldosteronism; PRA, plasma renin activity; RCT, randomized controlled trial; ROB, risk of bias; SIT, saline infusion test.

Primary aldosteronism (PA) represents the predominant yet frequently underrecognized endocrine etiology of secondary hypertension (1-3), with an estimated prevalence of approximately 5% to 14% among hypertensive individuals in primary care settings (4) and reaching up to 29.8% in specialized referral centers (5-7), particularly among individuals exhibiting specific clinical characteristics or comorbid conditions (8-11).

Primary aldosteronism is missed or misdiagnosed 95% of the time (12, 13). The delayed or missed diagnosis of PA is associated with poor blood pressure control in many hypertensive individuals (14). If left untreated, this can result in increased morbidity and mortality due to sustained elevation in blood pressure and aldosterone-mediated damage to target organs (15, 16). Conversely, achieving optimal blood pressure control and reducing cardiovascular-renal risks necessitate the implementation of targeted therapeutic strategies, which may include specific medical treatment or surgical adrenal intervention (17, 18).

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Diagnosis of PA involves a widely accessible and cost-effective screening blood test capable of identifying over 90% of cases (19, 20). However, only a small fraction of individuals with PA receive appropriate diagnosis and subsequent treatment (21).

Management options for PA exhibit considerable variability in terms of complexity and financial implications, encompassing approaches that range from comprehensive confirmatory testing to more straightforward medical therapy. The most meticulous approach involves adrenal venous sampling (AVS), adrenal imaging modalities, and confirmatory tests, all of which are essential for accurate diagnosis and treatment planning (22-24). Conversely, a less resource-intensive approach involves initiating treatment with mineralocorticoid receptor antagonists without extensive testing, which could be suitable for selected patient populations (23, 25-28). The determination of the management pathway ultimately relies on the availability of healthcare resources, patient-specific characteristics, and individual preferences, thereby emphasizing the need for tailored treatment strategies in the management of PA (24, 29).

The socio-economic implications of inadequately managing primary aldosteronism are substantial, primarily due to its correlation with increased incidence of cardiovascular disease and diabetes (30). Failure to provide appropriate treatment for PA may lead to critical health complications, underscoring the necessity for prompt diagnosis and intervention (31, 32).

In 2016, the Endocrine Society developed clinical practice guidelines to improve the care of individuals with PA (31). Since the release of this guideline, additional studies and systematic reviews have been published (33-37). The Endocrine Society has identified the need to update the guidelines for managing individuals with PA. This systematic review summarizes the evidence supporting the updated guideline.

Methods

This systematic review followed an a priori protocol developed by a guideline panel from the Endocrine Society on the management of PA. This report complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (38).

Eligibility Criteria

The panel members prioritized 10 questions addressing the management of PA in adult individuals. The 10 questions are presented using the PICO (population, intervention, comparator, and outcomes) format accompanied by the eligibility criteria in the supplement (eSupplementary Table S1) (39).

Data Sources and Search Strategies

A comprehensive search of several databases was performed on August 14, 2023, and updated on October 4, 2024. Results were limited to English Language. Databases searched (and their content coverage dates) were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1970+).

The search strategies were designed and conducted by a medical librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used to search for PA management and outcomes in adults. Additional references identified by the guideline committee were also considered. The complete list of search terms used and how they were combined is available in the appendix (eSupplementary Table S2) (39).

Study Selection

Two reviewers independently screened the titles and abstracts of candidate studies. If a study was deemed ineligible by a single reviewer, a second reviewer reassessed its eligibility. If a study was considered eligible by at least 1 reviewer, the full text was screened by 2 independent reviewers. Any disagreements were resolved by consensus or by a third reviewer.

Data Extraction

Data from the included studies were extracted by one reviewer and confirmed by an independent second reviewer for completeness and accuracy using a standardized form created by a web-based program (DistillerSR, Evidence Partners, Ottawa, Canada). When multiple reports from the same study dataset were published, the one with the largest dataset was included. If a study compared participants with PA to participants with essential hypertension, we considered the group of participants who had PA. For studies that reported baseline and outcomes based on the propensity score (before the match and after the match), we extracted the data for participants matched by propensity score. Elements of data extraction are presented in the appendix (eSupplementary Table S3) (39).

Data Synthesis and Analysis

Analyses were based on the intention-to-treat (ITT) principle for randomized controlled trials (RCTs) or the number of participants initially assigned to the interventions at the start of the study for observational studies. For continuous outcomes, we calculated the mean difference (MD). We calculated the odds ratio (OR) with 95% CI for binary outcomes and adverse events (ie, the odds of an event occurring in the intervention group compared to the comparison group). The DerSimonian and Laird random-effects method was used to combine effect sizes across the studies. We evaluated heterogeneity between studies using the I^2 indicator, low heterogeneity was considered to be $\leq$50%. Predefined subgroup analyses were conducted based on follow-up periods and unilateral primary aldosteronism. The analysis was conducted using the OpenMeta software package.

Methodologic Quality and Certainty of Evidence

The risk of bias (RoB) was assessed by 2 independent reviewers. The Cochrane Risk of Bias assessment tool version 2 (40) was used for RCTs, and the Newcastle-Ottawa scale (41) was used for nonrandomized studies. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to rate the certainty of evidence (42). RCTs start at a high certainty, and observational studies start at low certainty. The certainty of evidence is then downrated according to the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Study Selection

Electronic searches yielded 7700 citations (eSupplementary Table S2 (39)). An additional 84 references were identified through other sources, including cross-referencing of included studies and consultation with content experts. From these, 361 citations underwent full-text review, ultimately 95 studies (in 99 citations) met the inclusion criteria. The study selection process is illustrated in eSupplementary Fig. S1 (39). For each PICO, study characteristics, demographics, and intervention details are provided in eSupplementary Table S3 (39). The RoB assessment is presented in eSupplementary Table S4 (39). The results of meta-analysis outcomes are presented in Table 1.

Question 1: Should care with PA screening vs care without PA screening be used for all patients with hypertension?

One comparative observational study (43) with 269 010 participants reporting the outcome of systolic blood pressure level was included. Study characteristics and RoB are provided in eSupplementary Tables S3.1 (39) and S4.2 (39), respectively.

The testing for PA was uncommon and was associated with higher rates of evidence-based treatment with mineralocorticoid receptor antagonists (MRAs) and better longitudinal blood pressure control (very low certainty). The summary of findings is presented in eSupplementary Table S6 (39).

Question 2: Should PA-specific therapy (medical and surgical) vs nonspecific antihypertensive therapy be used in patients with PA?

Two comparative observational studies (37, 44) with 258 participants were included. The reported outcomes were systolic blood pressure level, daily dose of antihypertensive agents, and number of antihypertensive medications. Study characteristics and RoB are provided in eSupplementary Tables S3.2 and S4.2, respectively (39).

One observational study by Buffolo et al (37) showed that all participants who underwent unilateral adrenalectomy displayed complete biochemical outcomes at the 6-month follow-up. Participants who received MRAs showed a reduction of systolic and diastolic blood pressure with a nonsignificant increase in antihypertensive treatment. Conversely, participants who received general antihypertensive agents showed a reduction in systolic (very low certainty) and diastolic blood pressure at 6 months, accompanied by an increase in defined daily dose.

One observational study by Fourkiotis et al (44) showed that eplerenone treatment was associated with a lower potassium levels and a higher number of required antihypertensive medications compared to nonspecific antihypertensive therapy. There were no significant differences between the groups regarding ambulatory blood pressure and 24-hour blood pressure measurements except that the group without specific anti-mineralocorticoid therapy had significantly higher 24-hour systolic blood pressure levels, $P < .05$ (very low certainty). Medical therapy with spironolactone or eplerenone appears to be as effective as adrenalectomy in improving renal function and blood pressure control.

The summary of findings is presented in eSupplementary Table S6 (39).

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

We did not identify any studies that directly addressed this comparison.

Question 4: Should care guided by aldosterone suppression vs no aldosterone suppression be used in patients with positive PA screen prior to initiating PA-specific therapy (medical or surgical)?

One comparative observational study (45) with 199 participants was included. The reported outcomes were the percentage of individuals achieving blood pressure control and detection of unilateral PA. Study characteristics and RoB are provided in eSupplementary Tables S3.3 and S4.2, respectively (39).

There was a higher rate of hypertension cure among participants with a post-saline infusion test (SIT) aldosterone level higher than 277 pmol/L (10 ng/dL; $P = .16$) (very low certainty). The proportion of participants with lateralized AVS was 12 of 41 (29%) among those with post-SIT aldosterone <139 pmol/L (5 ng/dL) and 38 of 104 (37%) among those with post-SIT aldosterone <277 pmol/L (10 ng/dL) (very low certainty).

The summary of findings is presented in eSupplementary Table S6 (39).

Question 5: Should PA-specific medical therapy vs surgical therapy be used in patients with diagnosed PA?

A total of 4 RCTs (46-49) with 669 participants and 52 comparative observational studies (56 citations) (16, 22, 35, 37, 44, 50-100) with 17 893 participants were included. Study characteristics and RoB are provided in eSupplementary Tables S3.4 and S4.1-2, respectively (39).

Some studies compared participants with PA to participants with essential hypertension. We included in this analysis the group of participants who had PA.

Outcomes. Compared to surgical therapy, PA-specific medical therapy was associated with a higher systolic blood pressure levels (42 studies [46 citations]) (16, 22, 35, 37, 44, 50-56, 59-66, 69, 71, 72, 75-80, 82-89, 91-99) (MD: 4.811; 95% CI [3.327-6.294], low certainty); an increased number of antihypertensive agents at short-term follow-up (3 studies) (46-48) (MD: 1.348; 95% CI [0.866-1.830], moderate certainty) and long-term follow-up (20 studies [21 citations]) (22, 35, 44, 51, 53, 54, 60, 61, 64, 68, 76-78, 80, 82, 85, 87, 93, 95, 96, 98) (MD: 1.339; 95% CI [1.136-1.542], very low certainty); a higher dosage of antihypertensive agents (8 studies) (37, 51, 54, 56, 60, 64, 69, 96) (MD: 1.855; 95% CI [1.400-2.309], low certainty); stroke (2 studies) (57, 93) (OR: 1.821; 95% CI [1.144-2.898], low certainty); heart failure (3 studies) (16, 57, 93) (OR: 1.984; 95% CI [1.254-3.137], low certainty); and all-cause mortality

Table 1. Summary of meta-analysis

Question	Population	Intervention	Comparator	Outcome	Studies (n)	Population (n)	Effect (95% CI)	GRADE
5	Patients diagnosed with PA	PA-specific medical therapy	Surgical therapy	Achieving blood pressure control	20	3209	*OR 0.333 (0.202-0.550)	Low certainty
				Achieving blood pressure control	2	412	OR 0.950 (0.623-1.450)	Low certainty
				Achieving blood pressure control (unilateral PA)	2	264	OR 0.687 (0.415-1.137)	Low certainty
				Albuminuria	2	506	OR 2.781 (0.250-30.974)	Very low certainty
				All-cause mortality	6	4416	*OR 2.302 (1.367-3.879)	Low certainty
				Atrial fibrillation	5	2995	OR 1.247 (0.804-1.933)	Low certainty
				CKD	3	1352	OR 1.073 (0.555-2.075)	Very low certainty
				Diabetes	3	601	OR 1.259 (0.636-2.490)	Very low certainty
				Dosage of antihypertensive agents	8	1409	*MD (1.400-2.309)	Low certainty
				Dosage of antihypertensive agents	3	469	MD 2.478 (0.711-4.245)	Low certainty
				Dosage of antihypertensive agents (unilateral PA)	2	843	*MD 1.733 (1.160-2.306)	Low certainty
				Hypokalemia	4	1257	OR 0.498 (0.141-1.764)	Very low certainty
				Heart failure	3	2515	*OR 1.984 (1.254-3.137)	Low certainty
				Impaired glucose tolerance	2	92	OR 0.352 (0.119-1.041)	Very low certainty
				Ischemic heart disease	2	1657	OR 1.564 (0.873-2.802)	Very low certainty
				Major adverse cardiovascular events (MACE)	10	6099	OR 1.249 (0.856-1.822	Very low certainty
				Major adverse cardiovascular events (MACE)-unilateral PA	4	1683	OR 1.150 (0.463-2.855)	Very low certainty
				Medication adverse events	2	251	*OR 29.853 (3.726-239.166)	Very low certainty
				Number of antihypertensive agents	20	4998	*MD 1.339 (1.136-1.542)	Very low certainty
				Number of antihypertensive agents	3	425	*MD 1.348 (0.866-1.830)	Moderate certainty
				Proteinuria	2	613	OR 1.599 (0.935-2.736)	Very low certainty
				Reduction in eGFR	11	3918	MD 0.599 (−2.050 to 3.249)	Very low certainty
				Reduction in eGFR	2	285	MD 1.515 (−1.981 to 5.010)	Low certainty
				Stroke	2	1657	*OR 1.821 (1.144-2.898)	Low certainty
				Systolic blood pressure level	42	10 286	*MD 4.811 (3.327-6.294)	Low certainty
				Systolic blood pressure level	4	653	MD −0.111 (−2.943 to 2.721)	Very low certainty
				Systolic blood pressure level (unilateral PA)	6	1762	MD −0.844 (−8.636 to 6.948)	Low certainty
6	People with PA	AVS	Imaging (CT/MRI/MDCT)	Achieving blood pressure control	6	916	OR 1.068 (0.740-1.541)	Low certainty
				Biochemical cure rate post-adrenalectomy, complete	5	1226	OR 1.319 (0.550-3.165)	Very low certainty
				Biochemical cure rate post-adrenalectomy, partial	4	1070	OR 0.675 (0.401-1.136)	Very low certainty
				Biochemical cure rate post-adrenalectomy, missing	4	1070	*OR 0.266 (0.103-0.690)	Low certainty
				Detection of unilateral PA	25	13 053	OR 0.871 (0.664-1.143)	Very low certainty
				Dosage of antihypertensive agents	2	939	MD −0.248 (−0.738 to 0.242)	Very low certainty
				Number of antihypertensive agents	3	419	MD 0.119 (−0.099 to 0.337)	Low certainty
				Systolic blood pressure level	5	1358	MD −0.841 (−3.859 to 2.177)	Very low certainty

(*continued*)

Table 1. Continued

Question	Population	Intervention	Comparator	Outcome	Studies (n)	Population (n)	Effect (95% CI)	GRADE
7	Patients with PA receiving PA-specific medical therapy	Continued suppressed renin	Not suppressed renin	Atrial fibrillation	2	435	OR 1.164 (0.382-3.551)	Very low certainty
				Dosage of antihypertensive agents	6	2027	MD −0.060 (−0.747 to 0.627)	Very low certainty
				Major adverse cardiovascular events (MACE)	4	1749	OR 1.615 (0.746-3.495)	Very low certainty
				Number of antihypertensive agents	2	350	*MD 0.225 (0.015-0.435)	Very low certainty
				Reduction in eGFR	3	718	*MD −0.943 (−1.169 to −0.717)	Very low certainty
				Systolic blood pressure level	11	2887	MD 2.014 (−0.101 to 4.130)	Very low certainty
9	Patients with PA	Spironolactone	Other MRAs	Achieving blood pressure control	2	171	OR 1.652 (0.542-5.040)	Very low certainty
				Control of hypokalemia	2	155	MD 0.064 (−0.064 to 0.192)	Low certainty
				Hyperkalemia	2	135	OR 1.974 (0.188-20.687)	Low certainty
				Systolic blood pressure level	3	255	MD −3.604 (−20.012 to 12.805)	Very low certainty

Abbreviations: AVS, adrenal venous sampling; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; OR, odds ratio; PA, primary aldosteronism.
*Denotes statistically significant.

(6 studies) (16, 57, 74, 80, 81, 93) (OR: 2.302; 95% CI [1.367-3.879], low certainty).

Surgical therapy was associated with a better blood pressure control compared to medical therapy (20 studies [22 citations]) (22, 35, 54, 55, 58, 61, 65, 68-70, 73, 77, 80, 81, 83, 84, 86, 88-90, 92, 99) (OR: 0.333; 95% CI [0.202-0.550], low certainty).

No statistically significant differences were found for ischemic heart disease (2 studies) (57, 93) (OR: 1.564; 95% CI [0.873-2.802], very low certainty); atrial fibrillation (5 studies) (16, 54, 57, 71, 93) (OR: 1.247; 95% CI [0.804-1.933], low certainty); hypertension remission (1 study) (96) (OR: 1.385; 95% CI [0.39-4.918], very low certainty); major adverse cardiovascular events (MACE) (10 studies) (16, 59-61, 74, 76, 78, 80, 94, 95) (OR: 1.249; 95% CI [0.856-1.822], very low certainty); or cardiovascular mortality (1 study) (57) (OR: 6.886; 95% CI [0.827-57.343], very low certainty).

One cohort study (67) found that individuals with PA who underwent adrenalectomy had a lower incidence of new-onset atrial fibrillation (NOAF) compared to those receiving lower doses of MRA. In contrast, individuals on MRA therapy had a higher risk of mortality, major cardiac and cerebrovascular events, and combined NOAF with mortality.

One retrospective study (81) showed that targeted blood pressure of <140/90 was achieved in surgically treated individuals before discharge to the community, whereas medically treated individuals required a much longer-term follow-up to manage their condition.

The summary of findings is presented in eSupplementary Table S5.1a and eSupplementary Figs. S2.1a-I, S2.1a-IV, S2.1b-I, S2.1c-I, S2.1d-1, S2.1e, S2.1f-I, S2.1g, S2.1n-I, S2.1n-IV, S2.1o-I, S2.1o-III, S2.1p-I, and S2.1p-IV (39).

Adverse events. Compared to surgical therapy, medical therapy was associated with an increased risk of medication related adverse events (2 studies) (79, 82) (OR: 29.853; 95% CI [3.726-239.166], very low certainty); erectile dysfunction (1 study) (84) (OR: 23.78; 95% CI [1.316-429.559], very low certainty); and increased antiandrogenic adverse events, such as gynecomastia, mastopathy, menstrual disturbances, erectile dysfunction, and decreased libido (1 study) (47) (OR: 118.3; 95% CI [15.798-885.874], moderate certainty).

Compared to medical therapy, surgical therapy was associated with an increased total adverse events (1 study) (49) (OR: 0.514; 95% CI [0.286-0.922], moderate certainty).

One prospective study (3 citations) (83, 86, 88) found that among 21 male participants treated with spironolactone, 4 (19%) had clinically relevant breast engorgement that responded well to the reduction of dosage.

One retrospective study (96) reported adverse drug reactions in 13 out of 33 participants who received spironolactone. The specific adverse reactions included constipation (1/33), fatigue (1/33), gynecomastia (8/33), hypotension (2/33), low libido (2/33), and unspecified intolerance (2/33). Among participants who received eplerenone, vomiting was reported in 1 out of 8 participants. For participants who underwent adrenalectomy, the following adverse events were reported: permanent sensory loss at T12 (1/23), postoperative acute kidney injury (1/23), postoperative numbness (12/23), and readmission for transient postoperative pain (1/23). No intraoperative complications or perioperative mortality were observed.

One case-control study (94) reported 61 hospitalization events among 51 participants in the spironolactone intervention

group and 37 events among 33 participants in the surgical intervention group.

No statistically significant differences were found in albuminuria (2 studies) (79, 95) (OR: 2.782; 95% CI [0.250-30.974], very low certainty); chronic kidney disease (3 studies) (72, 79, 95) (OR: 1.073; 95% CI [0.555-2.075], very low certainty); diabetes (3 studies) (77, 89, 95) (OR: 1.259; 95% CI [0.636-2.490], very low certainty); deep vein thrombosis (DVT) (1 study) (90) (OR: 0.656; 95% CI [0.025-17.06], very low certainty); hypokalemia (4 studies) (54, 58, 60, 73) (OR: 0.498; 95% CI [0.141-1.764], very low certainty); inferior vena cava bleeding (1 study) (78) (OR: 0.719; 95% CI [0.028-18.207], very low certainty); proteinuria (2 studies) (60, 69) (OR: 1.599; 95% CI [0.935-2.736], very low certainty); reduction in estimated glomerular filtration rate (eGFR) (11 studies [12 citations]) (52, 54, 60, 62, 66, 69, 72, 73, 79, 93, 95, 100) (MD: 0.599; 95% CI [−2.050 to 3.249], very low certainty), and the other adverse events listed in eSupplementary Table S5.1b (39).

The summary of findings is presented in eSupplementary Table S5.1 and eSupplementary Figs. S2.1h, S2.1i, S2.1j-I, S2.1k, S2.l-II, S2.1m, S2.1q-III, and S2.1r (39).

Question 6: Should care guided by adrenal lateralization with computed tomography (CT) scanning and AVS vs CT scanning alone be used for deciding treatment approach in people with PA?

One RCT (48) with 200 participants and 29 comparative observational studies (22, 36, 82, 101-126) with 8375 participants were included. Study characteristics and RoB are provided in eSupplementary Tables S3.5 and S4.1-2, respectively (39).

Outcomes. Compared to AVS, CT scanning alone may be associated with a lower post-adrenalectomy biochemical cure rate (only in the group of missing cure type) (4 studies) (103, 104, 110, 124) (OR: 0.266; 95% CI [0.103-0.690], low certainty).

No statistically significant differences were found in achieving blood pressure control (6 studies) (36, 104, 105, 118, 122, 124) (OR: 1.068; 95% CI [0.740-1.541], very low certainty); biochemical cure rate post-adrenalectomy, complete (5 studies) (36, 103, 104, 110, 124) (OR: 1.319; 95% CI [0.550-3.165], very low certainty); biochemical cure rate post-adrenalectomy, partial (4 studies) (103, 104, 110, 124) (OR: 0.675; 95% CI [0.401-1.136], very low certainty); dosage of antihypertensive medications (2 studies) (110, 124) (MD: −0.248; 95% CI [−0.738 to 0.242], very low certainty), number of antihypertensive agents (3 studies) (104, 105, 117) (MD: 0.119; 95% CI [−0.099 to 0.337], low certainty); detection of unilateral PA (25 studies) (22, 36, 82, 101-103, 105-109, 111-121, 123, 125, 126) (OR: 0.871; 95% CI [0.664-1.143], very low certainty); or systolic blood pressure levels (5 studies) (104, 105, 110, 117, 124) (MD: −0.841; 95% CI [−3.859 to 2.177], very low certainty).

The summary of findings is presented in eSupplementary Table S5.2a and eSupplementary Figs. S2.2a-I, S2.2b-I, S2.2c-I, S2.2d-I, S2.2e-I, S2.2f-I, S2.2g-I, and S2.2h (39).

Adverse events. Compared to CT scan alone, AVS was associated with an increased risk of adrenal hemorrhage (1 study) (36) (OR: 23.491; 95% CI [1.096-503.597], very low certainty).

One RCT (48) reported the total adverse events in 175/131 (AVS) vs 150/131 (CT).

No statistically significant differences were found in atypical chest pain (1 study) (36) (OR: 13.582; 95% CI [0.539-342.363], very low certainty); or serious adverse events (1 study) (48), (OR: 1.37; 95% CI [0.56-3.36], moderate certainty).

The summary of findings is presented in eSupplementary Table S5.2b (39).

Question 7: Should continued suppressed renin vs not suppressed renin be used in patients with PA receiving PA-specific medical therapy?

A total of 11 (15, 16, 53, 56, 71, 127-132) comparative observational studies with 3967 participants were included. Study characteristics and RoB are provided in eSupplementary Tables S3.6 and S4.2, respectively (39).

Outcomes. Compared to unsuppressed plasma renin activity (PRA), suppressed PRA may be associated with an increased number of antihypertensive agents (2 studies) (53, 131) (MD: 0.225; 95% CI [0.015-0.435], very low certainty); an increased risk of stroke (1 study) (132) (OR: 5.684; 95% CI [1.181-27.365], very low certainty); an increased risk of atrial fibrillation at the longest follow-up (1 study) (71) (OR: 2.523; 95% CI [1.093-5.828], very low certainty); and it might be associated with increased mortality (1 study) (15) (OR: 3.45; 95% CI [1.02-11.68], very low certainty). Conversely, unsuppressed PRA may be associated with better control of hypokalemia compared to suppressed PRA (1 study) (132) (MD: −0.11; 95% CI [−0.201 to −0.019], very low certainty).

No statistically significant differences were found in major adverse cardiovascular events (MACE) (4 studies) (15, 16, 130, 131) (OR: 1.615; 95% CI [0.746-3.495], very low certainty); ischemic heart disease (1 study) (132) (OR: 4.08; 95% CI [0.418-39.803], very low certainty); heart failure (1 study) (132) (OR: 4.024; 95% CI [0.162-99.802], very low certainty); systolic blood pressure level (11 studies) (15, 16, 53, 56, 71, 127-132) (MD: 2.014; 95% CI [−0.101 to 4.130], very low certainty); dosage of antihypertensive agents (6 studies) (15, 56, 127, 129, 130, 132) (MD: −0.060; 95% CI [−0.747 to 0.627], very low certainty); cerebrovascular events (1 study) (131) (OR: 0.291; 95% CI [0.012-7.282], very low certainty); or cerebrocardiovascular events (1 study) (128) (OR: 1.571; 95% CI [0.029-85.417], very low certainty).

The summary of findings is presented in eSupplementary Table S5.3a and eSupplementary Figs. S2.3a-I, S2.3b-I, S2.3c-I, S2.3d, and S2.3f (39).

Adverse events. Unsuppressed renin may be associated with a smaller reduction in eGFR (3 studies) (127, 131, 132) (MD: −0.943; 95% CI [−1.169 to −0.717], very low certainty).

No statistically significant differences were found in chronic kidney disease (1 study) (131) (OR: 0.677; 95% CI [0.173-2.645], very low certainty); diabetes (1 study) (131)

(OR: 0.48; 95% CI [0.109-2.11], very low certainty); dyslipidemia (1 study) (131) (OR: 0.677; 95% CI [0.206-2.226], very low certainty); or obesity (1 study) (131) (OR: 0.769; 95% CI [0.145-4.085], very low certainty).

The summary of findings is presented in eSupplementary Table S5.4b and eSupplementary Fig. S2.3e (39).

Question 8: Should a dexamethasone suppression test vs no dexamethasone suppression test be used in patients with PA and adrenal adenoma?

We did not identify any studies that directly addressed this comparison.

Question 9: Should spironolactone vs other MRAs be used for medical treatment of PA?

A total of 3 RCTs (133-135) with 229 participants and 1 comparative observational study with 188 participants were included. Study characteristics and RoB are provided in eSupplementary Tables S3.7 and S4.1-2, respectively (39).

One RCT (136), published after the search date, compared spironolactone to finerenone. The study showed that finerenone demonstrates comparable efficacy to spironolactone in blood pressure control and hypokalemia management while maintaining a favorable safety profile in individuals with PA.

We excluded one study (137) that compared spironolactone to esaxerenone in Japan, due to the lack of FDA approval for esaxerenone in treating PA in the United States. The study outcomes included systolic blood pressure level, dosage of antihypertensive medications, serum potassium levels, and gynecomastia. Systolic blood pressure levels tended to decrease after 3 and 6 months of treatment in both the spironolactone and esaxerenone groups, with no significant differences observed between the 2 groups at either time point. Spironolactone was associated with a higher dosage of antihypertensive medications compared to esaxerenone at 3 months (MD: 37.41; 95% CI [36.42-38.40]) and 6 months (MD: 42.23; 95% CI [41.10-43.36]). Serum potassium levels were significantly higher in the spironolactone group than in the esaxerenone group at 3 and 6 months. No symptomatic adverse events were observed, apart from gynecomastia in one male patient in the spironolactone group.

Outcomes. Compared to eplerenone, spironolactone may be associated with control of hypokalemia at the longest follow-up duration (1 study) (44) (MD: 0.22; 95% CI [0.011-0.429], very low certainty).

Eplerenone may be associated with a higher number of antihypertensive agents (1 study) (44) (MD: −1.4; 95% CI [−2445 to −0.355], very low certainty); and an increased dosage of antihypertensive agents (1 study) (135) (MD: −41.7; 95% CI [−53.394 to −30.006], low certainty).

No statistically significant differences were found in achieving blood pressure control (2 studies) (133-135) (OR: 1.652; 95% CI [0.542-5.040], very low certainty) and the levels of systolic blood pressure (3 studies) (133-135) (MD: −3.604; 95% CI [−20.012 to 12.805], very low certainty).

The summary of findings is presented in eSupplementary Table S5.4a and eSupplementary Figs. S2.4a, S2.4c-I, and S2.4d-I (39).

Adverse events. Spironolactone was associated with an increased incidence of female breast pain (1 study) (134) (OR: 25.115; 95% CI [1.437-439.047], low certainty); and gynecomastia (1 study) (134) (OR: 5.756; 95% CI [1.205-27.488], low certainty).

No statistically significant differences were found for hyperkalemia (2 studies) (133, 134) (OR: 1.974; 95% CI [0.188-20.687], low certainty); impotence (1 study) (134) (OR: 6.456; 95% CI [0.325-128.299], low certainty); serious adverse events (1 study) (134) (OR: 0.323; 95% CI [0.06-1.75], low certainty); treatment-emergent adverse events (1 study) (134) (OR: 1.478; 95% CI [0.616-3.546], low certainty); and the other reported adverse events in eSupplementary Table S5.4b (39).

The summary of findings is presented in eSupplementary Table S5.4b and eSupplementary Figs. S2.4b (39).

Question 10: Should epithelial sodium channel inhibitors vs MRAs (steroidal and nonsteroidal) be used for medical treatment of PA?

We did not identify any studies that directly addressed this comparison.

Subgroup Analysis

A subgroup analysis based on follow-up periods and unilateral PA was performed when feasible.

The summary of findings is presented in eSupplementary Tables S5.1, S5.2, and S5.3 and eSupplementary Figs. S2.1, S2.2, S2.3, and S2.4 (39).

No significant credible findings were identified based on clinical characteristics.

Discussion

Main Findings

This systematic review summarized evidence to support the development of a clinical practice guideline on the management of primary aldosteronism by the Endocrine Society.

Despite PA being the most common cause of secondary hypertension, we found that screening for PA was suboptimal (43). Not surprisingly, testing for PA was associated with an overall better control of hypertension, likely due to a higher likelihood for an individualized therapy. Targeted therapy in PA currently includes adrenalectomy, with a goal of PA resolution, or MRA therapy.

Patients with PA may present with either unilateral or bilateral disease. When unilateral, adrenalectomy leads to PA resolution. Medical therapy with MRA is usually the standard of care for bilateral PA or in those who do not wish to pursue surgical therapy. Distinguishing between unilateral and bilateral PA may be challenging. AVS is a technically difficult and expensive procedure that is not widely available or universally successful. On the other hand, CT-based diagnosis of PA lateralization may not be accurate in those without clear adrenal adenoma, in those with bilateral adrenal nodules, or in those with an adenoma other than aldosteronoma. We found that when compared to AVS, a CT-based decision to proceed with adrenalectomy was associated with a lower rate of PA remission (103, 104, 110, 124).

The alternative to adrenalectomy is medical therapy targeting hypertension and/or targeting aldosterone action. While

general antihypertensive therapy can effectively reduce blood pressure, patients usually need to be treated with more medications. On the other hand, we found that using MRA therapy improved hypertension control without a significant increase in the medical therapy intensity (37, 44). Several MRAs are currently available to treat PA. Spironolactone is a longer-acting and more potent MRA that is most frequently used in PA. Eplerenone is a shorter-acting, less potent MRA with the advantage of lacking androgen receptor antagonism. Finally, a nonsteroidal MRA, finerenone, is a newer agent that has also been investigated in PA. When compared to eplerenone, spironolactone was more effective with hypokalemia control and was associated with less intensity in hypertension management (71, 135). A study that compared finerenone and spironolactone showed a similar efficacy in hypertension and hypokalemia management (136). Overall, MRA therapy has a favorable adverse event profile. We found that adverse events of spironolactone due to androgen receptor antagonism were most common, with gynecomastia, erectile dysfunction, and menstrual irregularities (47, 84, 134).

MRAs are usually titrated based on blood pressure and potassium levels, with several studies exploring renin as a potential biomarker of optimal MRA therapy. Suppressed renin is the hallmark of PA diagnosis, a reflection of autonomous (independent of renin) aldosterone secretion. In studies investigating patients treated with MRAs, those with suppressed renin plasma activity were more likely to need a higher number of antihypertensive medications, have persistent hypokalemia, and experience adverse outcomes, including stroke, atrial fibrillation, and mortality (53, 71, 131, 132).

When compared to adrenalectomy, we found that MRA therapy was less effective in improving hypertension, with higher blood pressure, number of antihypertensive agents, and dose of medications. Moreover, patients treated with MRAs had more frequent adverse outcomes, including stroke, heart failure, and mortality, than those treated with adrenalectomy. However, several caveats need to be considered, including suboptimal MRA therapy (with lower than effective dose), potential noncompliance, heterogeneity in the severity of PA between groups, and variable criteria for the selection of patients eligible for adrenalectomy.

The overall certainty of the available evidence is predominantly low to very low, which limits the strength of conclusions that can be drawn. Many of the included studies are observational, often with small sample sizes, inconsistent findings, or methodological limitations that increase the risk of bias. Furthermore, heterogeneity in study populations, interventions, and outcome measures complicates interpretation. As a result, while some patterns or associations may be observed, they should be interpreted with caution. High-quality, well-powered, randomized controlled trials are needed to provide more reliable evidence and support confident clinical decision-making.

Strengths and Limitations

The strengths of this systematic review relate to an a priori established protocol, comprehensive search of multiple databases, and collaboration with content experts from the Endocrine Society. Limitations relate to the nonrandomized nature of most of the included studies, the small number of available studies, and the lack of direct evidence for 3 out of 10 clinical questions identified to be critical for current practice.

Our systematic review targeted participants with primary aldosteronism and indeed 95% of the included studies have explicitly excluded participants with essential hypertension. Nevertheless, some studies may have included such participants.

Conclusion

The evidence summarized in this systematic review addresses various aspects of managing PA. These data will support the Endocrine Society's clinical practice guideline recommendations, along with other important decisional and contextual factors such as patients' values and preferences, feasibility, and acceptability.

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Data Availability

The original data generated and analyzed during this study are available in the repository listed in the references. The data supporting the findings of this study are openly accessible on *Figshare* (39).

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