


# Primary Aldosteronism Prevalence – An Unfolding Story

## Authors

Suranut Charoensri<sup>1,2</sup>, Adina F. Turcu<sup>1</sup> 

## Affiliations

- 1 Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan, USA. Ann Arbor, Michigan
- 2 Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand

## Key words

primary aldosteronism, hypertension, aldosterone, adrenal

received 30.01.2023

revised 09.03.2023

accepted 27.03.2023

published online 31.05.2023

## Bibliography

Exp Clin Endocrinol Diabetes 2023; 131: 394–401

DOI 10.1055/a-2066-2696

ISSN 0947-7349

© 2023. Thieme. All rights reserved.

Georg Thieme Verlag, Rüdigerstraße 14,  
70469 Stuttgart, Germany

## Correspondence

Adina F. Turcu, MD, MS

Division of Metabolism, Endocrinology and Diabetes,  
University of Michigan

1150 W Medical Center Drive

MSRB II, 5570B, Ann Arbor

MI, 48109

Tel.: 734-647-8906, Fax: 734-232-4839

aturcu@umich.edu

## ABSTRACT

Primary aldosteronism (PA) is characterized by dysregulated, renin-independent aldosterone excess. Long perceived as rare, PA has emerged as one of the most common causes of secondary hypertension. Failure to recognize and treat PA results in cardiovascular and renal complications, through processes mediated by both direct target tissue insults and indirectly, by hypertension. PA spans a continuum of dysregulated aldosterone secretion, which is typically recognized in late stages after treatment-resistant hypertension and cardiovascular and/or renal complications develop. Determining the precise disease burden remains challenging due to heterogeneity in testing, arbitrary thresholds, and populations studied. This review summarizes the reports on PA prevalence among the general population and in specific high-risk subgroups, highlighting the impact of rigid versus permissive criteria on PA prevalence perception.

## Introduction

Primary aldosteronism (PA) is a disorder of dysregulated aldosterone production that occurs independently from the physiological renin-angiotensin system. PA is a common and modifiable cause of secondary hypertension [1]. Compared with equivalent primary hypertension, PA has been associated with a disproportionately greater risk of cardiovascular, metabolic, and renal complications [2–7], mediated via inappropriate mineralocorticoid receptor (MR) activation within target tissues. Directed therapies, such as unilateral adrenalectomy or MR antagonists, have been shown to mitigate unfavorable outcomes in patients with PA [3, 8–11]. While determining the true prevalence of PA hinges on a number of varia-

bles, such as the population studied, clinical setting, tests, and criteria used to define PA [12–16], compelling evidence suggests that PA spans a spectrum of severity, of which only the very late stages are typically recognized. In this review, we discuss the reported frequency of PA across its pathophysiological spectrum and various populations at risk.

## The evolving definition of primary aldosteronism

In 1955, Dr. Jerome Conn published his clinical journey to solving the first documented case of PA in a 34-year-old woman with severe hypertension, profound hypokalemia, metabolic alkalosis, and intermittent tetany, which resolved after unilateral adrenalectomy

[17]. Although hypokalemia and metabolic alkalosis became hallmarks of PA, Dr. Conn acknowledged that such findings only capture the most severe forms of the disease. Moreover, as his expertise in PA evolved, Dr. Conn correctly anticipated that most patients with PA have normokalemic hypertension [18] and that the pathophysiology of PA might emerge in normotensive stages prior to clinically advanced manifestations [19, 20]. In the years that followed, numerous studies revealed the presence of autonomous aldosterone production among both hypertensive and normotensive individuals, supporting a broad spectrum of PA severity [21–24]. Following the introduction of the aldosterone-to-renin ratio (ARR) as a screening tool for PA in 1981, however, this initial paradigm of a PA severity continuum shifted towards a more pragmatic, binary disease classification [25]. Although intended to help standardize the diagnostic process, the diagnostic criteria for both ARR and the subsequently implemented confirmatory tests have been arbitrary and heterogeneous. An ARR of  $\geq 30$  (ng/dL)/(ng/mL/h), along with a plasma aldosterone concentration  $\geq 15$  ng/dL, constitute the most conservative criteria for a positive PA screening test [12]. Less stringent criteria increase the detection rates of both advanced and mild forms of PA [26–29]. Two recent systematic reviews of ARR testing found that the clinical performance of ARR varied widely with the patient population, clinical setting, and thresholds used, rendering sensitivities from 10% to 100% [30, 31].

Considering the dynamic fluctuations of renin and aldosterone in response to a large number of determinants [32–34], the current Endocrine Society guideline proposes confirmatory testing in most patients with positive screening results to solidify the PA diagnosis [12]. Notably, however, PA has been diagnosed in individuals with ARR values lower than the commonly used threshold for PA, indicating the limitations of arbitrary screening criteria in capturing the broad continuum of inappropriate aldosterone production. Using fludrocortisone-dexamethasone suppression tests, Markou et al. diagnosed PA in 13 of 100 normotensive women, regardless of baseline plasma aldosterone or ARR values, and 11 of these women developed hypertension within five years, supporting an incipient PA pathophysiology stage in these participants [35]. In a similar study, elevated 24-h urine aldosterone excretion suggestive of PA was found following oral sodium loading in a substantial number of individuals across the entire blood pressure spectrum, including in individuals with ARR considered normal [36]. Nevertheless, the definition of inappropriate aldosterone production relies, yet again, on arbitrary thresholds for each confirmation test. Variability in diagnostic tests and criteria explains inconsistencies in the reported prevalence of PA, which varied from 3.2% to 12.7% in the primary care setting, and from 1% to 29.8% in referral centers [37].

Beyond the heterogeneity of the diagnostic tests, PA prevalence reports also differ across various populations. Generally, the risk of PA is highest in patients with severe hypertension, and hypertension and hypokalemia. High PA prevalence has also been reported in individuals with hypertension and adrenal nodules, obstructive sleep apnea (OSA), or a family history of PA, and several expert guidelines recommended PA screening in these populations [12, 38–40].

## The reported prevalence of overt primary aldosteronism in treatment-resistant hypertension

Although reports of PA prevalence among patients with hypertension have been heterogeneous due to the vast differences in PA definition between studies, findings consistently suggest that PA prevalence increases in parallel with hypertension severity, ranging from 11–22% in the individual with treatment-resistant hypertension (► **Table 1**) [14, 27, 36, 41–46]. On average, only under 3–4% of individuals with treatment-resistant hypertension are screened for PA [14, 16, 47, 48]. When conducted, PA screening usually targets patients with multiple risk factors and those who have already developed cardiovascular and renal complications [47]. Physicians with secondary hypertension expertise, including endocrinologists and nephrologists, who typically also perform confirmatory testing and oversee the management of PA, are more likely to consider and screen for PA than primary care providers [48]. As very few patients with hypertension are referred to specialists, the true prevalence of PA across hypertension stages in the general population remains uncertain. In a meta-analysis of 39 studies of adults with hypertension, the weighted mean prevalence of overt PA was 5.5% for high-normal blood pressure, 4.2% for stage 1-, 10.2% for stage 2-, and 16.4% for stage 3 hypertension [37].

## The reported prevalence of overt primary aldosteronism in normotension and mild hypertension

Current guideline-directed PA screening may overlook milder cases of autonomous aldosterone production in the pathophysiological continuum of PA, which results in an underestimation of its prevalence among individuals with mild hypertension. Ito and colleagues performed systematic screening of PA during annual health examinations in adults without hypertension and found that 22.7% of prehypertensive subjects (BP 120–139/80–89 mmHg) had a positive ARR screening, and 6.8% had confirmed PA with captopril suppression test [49]. Other observational studies have provided evidence for PA in a subset of individuals with normal or mildly elevated blood pressure (► **Table 1**). Importantly, these unrecognized yet biochemically overt PA forms have been linked to unfavorable outcomes. During a four-year observation period in the Framingham Offspring Study, normotensive participants with higher aldosterone levels were more likely to develop incident and worsening hypertension [50]. Similar studies revealed that normotensive participants with suppressed plasma renin activity had a significantly higher risk of developing incident hypertension when compared with those without suppressed renin [51, 52]. These results indirectly suggest that early detection of autonomous aldosterone secretion and targeted therapeutic measures might mitigate cardiovascular complications mediated by inappropriate MR activation. However, the paucity of data on the cost-effectiveness of early screening and directed therapy make strategic interventions of uncertain value in early hypertension stages.

## The reported prevalence of overt primary aldosteronism in patients with hypokalemia

Numerous reports have assessed the prevalence of hypokalemia in patients with overt PA. In a meta-analysis of 39 observational stud-

► **Table 1** Studies of overt primary aldosteronism prevalence across the blood pressure spectrum.

Reference	Criteria	Study population	Prevalence of overt PA
Calhoun 2002 [41]	PRA < 1 ng/mL/h <b>AND</b> Positive oral sodium suppression test	Resistant hypertension	20 %
Mosso 2003 [42]	ARR > 25 (ng/dL)/(ng/mL/h) <b>AND</b> Positive fludrocortisone suppression test	Hypertension (overall)	6.10 %
		Stage 1 hypertension	2 %
		Stage 2 hypertension	8 %
		Stage 3 hypertension	13.20 %
Rossi 2006 [43]	ARR ≥ 40 (ng/dL)/(ng/mL/h) <b>AND</b> Positive captopril challenge test and/or LDF score <sup>#</sup> ≥ 0.5	Hypertension (overall)	11.20 %
		Stage 1 hypertension	6.60 %
		Stage 2 hypertension	15.50 %
		Stage 3 hypertension	19 %
Douma 2008 [44]	ARR > 20 (ng/dL)/(ng/mL/h) * with ALD > 15 ng/dL * <b>AND</b> Positive saline and fludrocortisone suppression test <b>AND</b> Responsive to spironolactone	Resistant hypertension	11.30 %
Ito 2011 [49]	ARR > 20 (ng/dL)/(ng/mL/h) <b>AND</b> Positive captopril challenge test	Prehypertension	6.80 %
		Stage 1 hypertension	3.30 %
Markou 2013 [35]	Positive fludrocortisone-dexamethasone suppression test	Normotension	13 %
Galati 2016 [45]	ARR > 20 (ng/dL)/(ng/mL/h) with ALD > 10 ng/dL with PRA < 1 ng/mL/h	Hypertension (overall)	4.70 %
		Resistant hypertension	10.50 %
Monticone 2017 [27]	ARR > 30 (ng/dL)/(ng/mL/h) with ALD > 10 ng/dL <b>AND</b> Positive saline infusion or captopril challenge test	Hypertension (overall)	5.90 %
		Stage 1 hypertension	3.90 %
		Stage 2 hypertension	9.70 %
		Stage 3 hypertension	11.80 %
Brown 2020 [36]	Positive oral sodium suppression test with post-test urine ALD ≥ 12 µg/day	Normotension	11.30 %
		Stage 1 hypertension	15.70 %
		Stage 2 hypertension	21.60 %
		Stage 3 hypertension	22 %
Xu 2021 [46]	ARR ≥ 30 (ng/dL)/(ng/mL/h) * with ALD > 10 ng/dL <b>AND</b> Positive saline infusion or captopril challenge test	Hypertension (overall)	3.30 %
		Stage 1 hypertension	0.70 %
		Stage 2 hypertension	3.40 %
		Stage 3 hypertension	12.60 %
Zekarias 2022 [14]	ARR ≥ 30 (ng/dL)/(ng/mL/h) with ALD ≥ 10 ng/dL	Resistant hypertension	16.90 %

<sup>#</sup>Logistic discriminant function (LDF) score was described elsewhere. [97]; \* ARR or ALD values have been converted to common units of measurement for ease of comparison.; Abbreviation; ARR, aldosterone-renin-ratio; ALD, aldosterone; PA, primary aldosteronism; PRA, plasma renin activity; LDF, logistic discriminant function.

ies, hypokalemia was presented in 0–37.5 % of patients with PA seen in primary care and 0–67 % of those from referral centers [37], with the highest proportion in patients with aldosterone-producing adenoma [43]. In contrast, the prevalence of PA among individuals with hypertension and hypokalemia has been poorly studied. Burrello and colleagues [53] retrospectively reviewed the medical records of 840 hypertensive patients with at least a single episode of hypokalemia (potassium level < 3.7 mmol/L) and found that the rates of overt PA increased with the decreasing serum potassium levels. Overt PA was diagnosed in 28.1 % of the overall cohort and in 88.5 % of patients with severe hypokalemia (potassium level < 2.5 mmol/L). Additionally, patients with spontaneous hypokalemia had overt PA more often than those with diuretic-induced hypokalemia (37.4 % versus 16.5 %, respectively) [53].

Hypokalemia was previously viewed as a hallmark of advanced PA [12]. Several reports, however, present normotensive patients diagnosed with hypokalemia prior to recognized PA [54–57]. The

mechanism underlying this entity is poorly understood. High vascular compliance, and an adaptive increase in renal sodium excretion in response to aldosterone excess, to maintain normal blood pressure, have been proposed as possible mechanisms [57]. Since PA has not been systematically screened in patients with isolated hypokalemia without hypertension, the prevalence of normotensive hypokalemic PA remains unknown.

### The reported prevalence of overt primary aldosteronism in patients with adrenal incidentaloma

In observational studies of patients with adrenal incidentaloma, the reported prevalence of overt PA ranges between 1 and 30 %, depending on the study design and the applied diagnostic criteria (► **Table 2**) [58–67]. Although overt PA is more frequently found in patients with adrenal incidentaloma and hypertension than in normotensives [12, 68–70], it should be emphasized that adrenal

► **Table 2** Studies of overt primary aldosteronism prevalence in patients with adrenal incidentaloma.

Reference	Criteria	Study population	Prevalence of overt PA
Mantero 2000 [58]	ARR elevation and suppressed PRA	Adrenal incidentaloma with exclusion of severe hypertension and hypokalemia	1.6% (all were hypertensive)
Bernini 2002 [59]	ARR > 20 (ng/dL)/(ng/mL/h) * AND Positive saline suppression or captopril challenge test	Adrenal incidentaloma with exclusion of hypokalemia	4% (all were hypertensive), 5.5% of hypertensive patients
Kim 2005 [60]	Not specified	Adrenal incidentaloma	10% (all were hypertensive), 25% of hypertensive patients
Comlekci 2010 [61]	ARR > 25 (ng/dL)/(ng/mL/h) AND Positive saline Suppression test	Adrenal incidentaloma with hypertension	4.4%
Kim 2013 [62]	ARR > 20 (ng/dL)/(ng/mL/h)	Adrenal incidentaloma	4.6%
Patrova 2015 [63]	ARR (not specified threshold)	Adrenal incidentaloma with hypertension	1.4%
Tabuchi 2016 [64]	ARR > 20 (ng/dL)/(ng/mL/h) AND Positive one of the confirmation tests	Adrenal incidentaloma	10.7% (93.3% were hypertensive)
Stavropoulos 2018 [65]	Positive saline suppression test with post-test ALD ≥ 6 ng/dL	Adrenal incidentaloma	3.35% (all were hypertensive)
Jing 2022 [66]	ARR (not specified threshold) AND Positive saline suppression or captopril challenge test	Adrenal incidentaloma	11.8% (76% were hypertensive and 12% were hypokalemia), 23.2% of hypertensive patients, 75% of hypokalemia patients
Kmieć 2022 [67]	ARR > 20 (ng/dL)/(ng/mL/h) * with ALD > 4 ng/dL	Adrenal incidentaloma with exclusion of overt PA	25.4% (56.3% were hypertensive) 24.3% of hypertensive patients
* ARR or ALD values have been converted to common units of measurement for ease of comparison.; Abbreviation; ARR, aldosterone-renin-ratio; ALD, aldosterone; PRA, plasma renin activity; PA, primary aldosteronism.			

incidentalomas are not always the source of aldosterone. Several studies have found high discrepancy rates between imaging findings and adrenal vein sampling (AVS) results [71–73]. Moreover, immunohistochemistry targeting aldosterone synthase (CYP11B2) has demonstrated that macroscopic nodules do not always produce aldosterone [74]. Conversely, microscopic CYP11B2-positive areas are not uncommon in patients with overt PA, including when cross-sectional imaging detects no adrenal abnormalities [75, 76].

An unresolved question regarding the evaluation of adrenal incidentaloma is whether we should screen for autonomous aldosterone production in patients who do not have hypertension. It has been suggested that biochemically overt PA is not rare in patients with adrenal incidentaloma and normal blood pressure [77, 78]. Kmieć and colleagues conducted a prospective study attempting to detect subclinical autonomous aldosterone secretion in patients with adrenal incidentaloma by using permissive criteria of ARR > 1.2 (ng/dL)/(mIU/L) (approximately 10 (ng/dL)/(ng/mL/h)) and plasma aldosterone concentration > 4 ng/dL. Normotensive patients with urine aldosterone excretion > 10 µg/day were considered to have mild autonomous aldosterone secretion, while hypertensive patients with urine aldosterone > 12 µg/day were diagnosed with overt PA. Overall, 25.4% of individuals with adrenal incidentaloma were found to have mild autonomous aldosterone secretion (24.3% among hypertensive and 26.9% in normotensive participants) [67].

### The reported prevalence of overt primary aldosteronism in patients with obstructive sleep apnea

The pathophysiology of OSA has been associated with alterations in the renin-angiotensin-aldosterone system [79]. Studies in animal models suggest that intermittent hypoxia and acute hypercapnia, as observed in OSA, are linked to elevated plasma aldosterone, independently of plasma renin activity [80]. Nonetheless, whether these changes contributed to a higher prevalence of overt PA in patients with OSA remains debatable (► **Table 3**). In an Italian study of individuals newly diagnosed with hypertension, patients with OSA confirmed with polysomnography had a much greater prevalence of overt PA (34%) than those without OSA (9.8%) [81]. Another single-center study in Poland showed a 21.3% PA prevalence in 94 patients with hypertension and moderate to severe OSA [82]. In contrast, a substantially lower prevalence of overt PA (8.9%) was reported in the HYPNOS trial, a multi-ethnic cohort study of 203 patients with OSA [83], suggesting that the prevalence of biochemically overt PA among individuals with OSA is comparable to other difficult-to-control hypertensive populations, questioning the current Endocrine Society recommendation to screen patients with OSA for PA. An important caveat of the HYPNOS trial, however, is the heterogeneity of laboratory assays and confirmatory tests used across the seven participating centers from four countries. In addition, the Apnea-Hypopnea Index employed in the HYPNOS trial was derived from cardiorespiratory polygraphy, which is not the

► **Table 3** Studies of overt primary aldosteronism prevalence in patients with obstructive sleep apnea (OSA) and hypertension.

Reference	Criteria	Study population	Prevalence of overt PA
Di Murro 2010 [81]	ARR > 40 (ng/dL)/(ng/mL/h) with ALD > 15 ng/dL with a suppressed renin	Hypertension with and without OSA	34% in OSA, 9.8% in non-OSA
Buffolo 2019 [83]	According to the Endocrine Society guideline	Hypertension with OSA	8.9%
Dobrowolski 2021 [82]	Positive saline suppression test with post-test ALD > 10 ng/dL	Hypertension with and without moderate to severe OSA	21.3% in moderate to severe OSA, 8% in non-moderate to severe OSA
Chee 2021 [85]	ARR > 20 (ng/dL)/(ng/mL/h) * or renin is suppressed or low, together with an adrenal adenoma	Hypertension with OSA	Likely PA; 5%, Possible PA; 30%

\* ARR or ALD values have been converted to common units of measurement for ease of comparison.; Abbreviation; ARR, aldosterone-renin-ratio; ALD, aldosterone; OSA, obstructive sleep apnea; PA, primary aldosteronism.

gold standard for OSA diagnosis [84]. In an Australian study, only 2 (5%) of 40 participants with OSA and hypertension were identified to have "likely PA" based on ARR. Additionally, 30% of patients were thought to have "possible PA" based on low renin and normal ARR in the context of interfering medications [85]. Nevertheless, Chomsky et al. estimated that screening for PA in patients with OSA remains cost-effective even if it detects only 3% of new PA cases [86]. Therefore, in light of the currently available evidence, the recommendation to screen for PA in patients with OSA is still reasonable. Further studies with standardized protocols are required to characterize the association between PA and OSA.

### The reported prevalence of overt primary aldosteronism in young adults with hypertension

Secondary hypertension should be considered in individuals with early-onset hypertension [87]. PA testing, however, is not recommended routinely in young adults [12, 88]. As such, data on the prevalence of overt PA in young adults are scarce. A prospective observational study conducted in India among adults under age 40 at hypertension onset revealed that 18.8% of participants had positive ARR screening results, and 17.8% overt PA was confirmed by saline suppression test. The recorded prevalence of overt PA was highest in people with hypertension onset at 30–39 years [89]. A 10-year delay between the initial hypertension diagnosis and PA confirmation was noted, suggesting that PA screening should be conducted in patients with early-onset hypertension.

### Other conditions associated with primary aldosteronism

Atrial fibrillation has emerged as one of the cardiovascular complications associated with PA. A meta-analysis found atrial fibrillation

to be 3.52 times more likely in patients with overt PA than in those with primary hypertension [2]. Nguyen and colleagues performed PA testing among 300 consecutive patients with hemorrhagic or ischemic stroke and found overt PA in 30% of patients with hypertension and atrial fibrillation, compared to 11.1% in the subgroup with treatment-resistant hypertension and 13.3% in those with hypertension and hypokalemia [90]. Another observational study found that overt PA was highly prevalent (42.5%) in participants with atrial fibrillation and no other identifiable causes of arrhythmia, such as structural heart defect or coronary artery disease, suggesting that overt PA might have led to atrial fibrillation in these patients [91]. Current guidelines do not yet endorse screening for PA in patients with atrial fibrillation [12, 38]. Stroke [92, 93], diabetes mellitus [94, 95], and obesity [96] are other disorders associated with overt PA. Further epidemiologic and mechanistic studies are needed to understand these associations prior to expanding PA screening recommendations.

## Conclusions

With our expanding understanding of PA pathophysiology and associated multi-system burden, the definition of PA has evolved, to include earlier stages of dysregulated aldosterone production. In parallel, timely testing for overt PA in at-risk populations is likely to uncover various degrees of renin-independent aldosterone excess at even higher than currently recognized rates. Initiatives to increase awareness of the clinical relevance of PA, to define PA across its continuum, and to develop decision algorithms, among others, would encourage the busy clinician to consider PA as a common cause of hypertension.

## Funding Information

Doris Duke Charitable Foundation — <http://dx.doi.org/10.13039/100000862>; 2019087

National Heart, Lung, and Blood Institute — <http://dx.doi.org/10.13039/100000050>; 1R01HL15583401

## Sources of Funding

AFT was supported by grants 2019087 from the Doris Duke Charitable Foundation; and 1R01HL15583401 from the National Heart, Lung, and Blood Institute.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- [1] Wannachalee T, Lieberman L, Turcu AF High prevalence of autonomous aldosterone production in hypertension: How to identify and treat it. *Curr Hypertens Rep* 2022; 24: 123–132. DOI: 10.1007/s11906-022-01176-7

- [2] Monticone S, D'Ascenzo F, Moretti C et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2018; 6: 41–50. DOI: 10.1016/S2213-8587(17)30319-4
- [3] Hundemer GL, Curhan GC, Yozamp N et al. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: A retrospective cohort study. *Lancet Diabetes Endocrinol* 2018; 6: 51–59. DOI: 10.1016/S2213-8587(17)30367-4
- [4] Mulatero P, Monticone S, Bertello C et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. *J Clin Endocrinol Metab* 2013; 98: 4826–4833. DOI: 10.1210/jc.2013-2805
- [5] Salcuni AS, Carnevale V, Battista C et al. Primary aldosteronism as a cause of secondary osteoporosis. *Eur J Endocrinol* 2017; 177: 431–437. DOI: 10.1530/EJE-17-0417
- [6] Reincke M, Rump LC, Quinkler M et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. *J Clin Endocrinol Metab* 2009; 94: 869–875. DOI: 10.1210/jc.2008-1851
- [7] Sechi LA, Novello M, Lapenna R et al. Long-term renal outcomes in patients with primary aldosteronism. *JAMA* 2006; 295: 2638–2645. DOI: 10.1001/jama.295.22.2638
- [8] Wu V-C, Wang S-M, Huang K-H et al. Long-term mortality and cardiovascular events in patients with unilateral primary aldosteronism after targeted treatments. *Eur J Endocrinol* 2021; 186: 195–205. DOI: 10.1530/EJE-21-0836
- [9] Rossi GP, Maiolino G, Flego A et al. Adrenalectomy lowers incident atrial fibrillation in primary aldosteronism patients at long term. *Hypertension* 2018; 71: 585–591. DOI: 10.1161/HYPERTENSIONAHA.117.10596
- [10] Chen Y-Y, Lin Y-HH, Huang W-C et al. Adrenalectomy improves the long-term risk of end-stage renal disease and mortality of primary aldosteronism. *J Endocr Soc* 2019; 3: 1110–1126. DOI: 10.1210/je.2019-00019
- [11] Hundemer GL, Curhan GC, Yozamp N et al. Renal outcomes in medically and surgically treated primary aldosteronism. *Hypertension* 2018; 72: 658–666. DOI: 10.1161/HYPERTENSIONAHA.118.11568
- [12] Funder JW, Carey RM, Mantero F et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101: 1889–1916. DOI: 10.1210/jc.2015-4061
- [13] Huang W-C, Lin Y-H, Wu V-C et al. Who should be screened for primary aldosteronism? A comprehensive review of current evidence. *J Clin Hypertens (Greenwich)* 2022; 24: 1194–1203. DOI: 10.1111/jch.14558
- [14] Zekarias K, Tessier KM Screening rate for primary aldosteronism among patients with apparent treatment-resistant hypertension: Retrospective analysis of current practice. *Endocr Pract* 2022; 28: 271–275. DOI: 10.1016/j.eprac.2021.11.085
- [15] Hundemer GL, Kline GA, Leung AA How common is primary aldosteronism? *Curr Opin Nephrol Hypertens* 2021; 30: 353–360. DOI: 10.1097/MNH.0000000000000702
- [16] Jaffe G, Gray Z, Krishnan G et al. Screening rates for primary aldosteronism in resistant hypertension: A cohort study. *Hypertension* 2020; 75: 650–659. DOI: 10.1161/HYPERTENSIONAHA.119.14359
- [17] Conn JW Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* 1955; 45: 3–17
- [18] Conn JW Evolution of primary aldosteronism as a highly specific clinical entity. *J Am Med Assoc* 1960; 172: 1650–1653. DOI: 10.1001/jama.1960.63020150008016
- [19] Conn JW Plasma renin activity in primary aldosteronism. Importance in differential diagnosis and in research of essential hypertension. *JAMA* 1964; 190: 222–225
- [20] Conn JW, Rovner DR, Cohen EL Normal and altered function of the renin-angiotensin-aldosterone system in man: Applications in clinical and research medicine. *Ann Intern Med* 1965; 63: 266–284. DOI: 10.7326/0003-4819-63-2-266
- [21] Channick BJ, Adlin EV, Marks AD Suppressed plasma renin activity in hypertension. *Arch Intern Med* 1969; 123: 131–140
- [22] Grim CE Editorial: Low renin "essential" hypertension; a variant of classic primary aldosteronism? *Arch Intern Med* 1975; 135: 347–350
- [23] Padfield PL, Brown JJ, Lever AF et al. Is low-renin hypertension a stage in the development of essential hypertension or a diagnostic entity? *Lancet* 1975; 1: 548–550. DOI: 10.1016/s0140-6736(75)91559-7
- [24] Adlin EV Letter: Plasma-renin and blood-pressure. *Lancet* 1975; 1: 699. DOI: 10.1016/s0140-6736(75)91814-0
- [25] Hiramatsu K, Yamada T, Yukimura Y et al. A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Results in hypertensive patients. *Arch Intern Med* 1981; 141: 1589–1593
- [26] Vaidya A, Mulatero P, Baudrand R et al. The expanding spectrum of primary aldosteronism: Implications for diagnosis, pathogenesis, and treatment. *Endocr Rev* 2018; 39: 1057–1088. DOI: 10.1210/er.2018-00139
- [27] Monticone S, Burrello J, Tizzani D et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. *J Am Coll Cardiol* 2017; 69: 1811–1820. DOI: 10.1016/j.jacc.2017.01.052
- [28] Stowasser M, Ahmed AH, Pimenta E et al. Factors affecting the aldosterone/renin ratio. *Horm Metab Res* 2012; 44: 170–176. DOI: 10.1055/s-0031-1295460
- [29] Baudrand R, Guarda FJ, Torrey J et al. Dietary sodium restriction increases the risk of misinterpreting mild cases of primary aldosteronism. *J Clin Endocrinol Metab* 2016; 101: 3989–3996. DOI: 10.1210/jc.2016-1963
- [30] Ariens J, Horvath AR, Yang J et al. Performance of the aldosterone-to-renin ratio as a screening test for primary aldosteronism in primary care. *Endocrine* 2022; 77: 11–20. DOI: 10.1007/s12020-022-03084-x
- [31] Hung A, Ahmed S, Gupta A et al. Performance of the aldosterone to renin ratio as a screening test for primary aldosteronism. *J Clin Endocrinol Metab* 2021; 106: 2423–2435. DOI: 10.1210/clinem/dgab348
- [32] Ng E, Gwini SM, Libianto R et al. Aldosterone, renin, and aldosterone-to-renin ratio variability in screening for primary aldosteronism. *J Clin Endocrinol Metab* 2022; 108: 33–41. DOI: 10.1210/clinem/dgac568
- [33] Maciel AAW, Freitas TC, Fagundes GFC et al. Intraindividual variability of serum aldosterone and its implication for primary aldosteronism screening. *J Clin Endocrinol Metab* 2022; dgac679. DOI: 10.1210/clinem/dgac679
- [34] Yozamp N, Hundemer GL, Moussa M et al. Intraindividual variability of aldosterone concentrations in primary aldosteronism: Implications for case detection. *Hypertension* 2021; 77: 891–899. DOI: 10.1161/HYPERTENSIONAHA.120.16429
- [35] Markou A, Pappa T, Kaltsas G et al. Evidence of primary aldosteronism in a predominantly female cohort of normotensive individuals: A very high odds ratio for progression into arterial hypertension. *J Clin Endocrinol Metab* 2013; 98: 1409–1416. DOI: 10.1210/jc.2012-3353
- [36] Brown JM, Siddiqui M, Calhoun DA et al. The unrecognized prevalence of primary aldosteronism: A cross-sectional study. *Ann Intern Med* 2020; 173: 10–20. DOI: 10.7326/M20-0065
- [37] Käyser SC, Dekkers T, Groenewoud HJ et al. Study heterogeneity and estimation of prevalence of primary aldosteronism: A systematic review and meta-regression analysis. *J Clin Endocrinol Metab* 2016; 101: 2826–2835. DOI: 10.1210/jc.2016-1472



- [38] Vaidya A, Malchoff CD, Auchus RJ et al. An individualized approach to the evaluation and management of primary aldosteronism. *Endocr Pract* 2017; 23: 680–689. DOI: 10.4158/EP161717.RA
- [39] Mulatero P, Monticone S, Deinum J et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: A position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. *J Hypertens* 2020; 38: 1919–1928. DOI: 10.1097/HJH.0000000000002510
- [40] Naruse M, Katabami T, Shibata H et al. Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021. *Endocr J* 2022; 69: 327–359. DOI: 10.1507/endocrj.EJ21-0508
- [41] Calhoun DA, Nishizaka MK, Zaman MA et al. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 2002; 40: 892–896. DOI: 10.1161/01.hyp.0000040261.30455.b6
- [42] Mosso L, Carvajal C, González A et al. Primary aldosteronism and hypertensive disease. *Hypertension* 2003; 42: 161–165. DOI: 10.1161/01.HYP.0000079505.25750.11
- [43] Rossi GP, Bernini G, Caliumi C et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006; 48: 2293–2300. DOI: 10.1016/j.jacc.2006.07.059
- [44] Douma S, Petidis K, Doumas M et al. Prevalence of primary hyperaldosteronism in resistant hypertension: A retrospective observational study. *Lancet* 2008; 371: 1921–1926. DOI: 10.1016/S0140-6736(08)60834-X
- [45] Galati S-J, Cheesman KC, Springer-Miller R et al. Prevalence of primary aldosteronism in an urban hypertensive population. *Endocr Pract* 2016; 22: 1296–1302. DOI: 10.4158/EP161332.OR
- [46] Xu F, Gao Z, Wang G et al. Prevalence, subtype classification, and outcomes of treatment of primary aldosteronism: A prospective study in China. *Endocr Pract* 2021; 27: 478–483. DOI: 10.1016/j.eprac.2020.10.007
- [47] Turcu AF, Nhan W, Grigoryan S et al. Primary aldosteronism screening rates differ with sex, race, and comorbidities. *J Am Heart Assoc* 2022; 11: e025952. DOI: 10.1161/JAHA.122.025952
- [48] Cohen JB, Cohen DL, Herman DS et al. Testing for primary aldosteronism and mineralocorticoid receptor antagonist use among U.S. veterans: A retrospective cohort study. *Ann Intern Med* 2021; 174: 289–297. DOI: 10.7326/M20-4873
- [49] Ito Y, Takeda R, Karashima S et al. Prevalence of primary aldosteronism among prehypertensive and stage 1 hypertensive subjects. *Hypertens Res* 2011; 34: 98–102. DOI: 10.1038/hr.2010.166
- [50] Vasan RS, Evans JC, Larson MG et al. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med* 2004; 351: 33–41. DOI: 10.1056/NEJMoa033263
- [51] Hu J, Shen H, Huo P et al. Heightened cardiovascular risk in hypertension associated with renin-independent aldosteronism versus renin-dependent aldosteronism: A collaborative study. *J Am Heart Assoc* 2021; 10: e023082. DOI: 10.1161/JAHA.121.023082
- [52] Brown JM, Robinson-Cohen C, Luque-Fernandez MA et al. The spectrum of subclinical primary aldosteronism and incident hypertension: A cohort study. *Ann Intern Med* 2017; 167: 630–641. DOI: 10.7326/M17-0882
- [53] Burrello J, Monticone S, Losano I et al. Prevalence of hypokalemia and primary aldosteronism in 5100 patients referred to a tertiary hypertension unit. *Hypertension* 2020; 75: 1025–1033. DOI: 10.1161/HYPERTENSIONAHA.119.14063
- [54] Médeau V, Moreau F, Trinquart L et al. Clinical and biochemical characteristics of normotensive patients with primary aldosteronism: A comparison with hypertensive cases. *Clin Endocrinol (Oxf)* 2008; 69: 20–28. DOI: 10.1111/j.1365-2265.2008.03213.x
- [55] Tang A, Pasieka J, Kline G Normotensive hypokalemic primary aldosteronism: How is this possible? *Endocrine Abstracts* 2018; 55: P26
- [56] Huang Y-C, Tsai M-H, Fang Y-W et al. Normotensive hypokalemic primary hyperaldosteronism mimicking clinical features of anorexia nervosa in a young patient. *Medicine (Baltimore)* 2020; 99: e20826. DOI: 10.1097/MD.00000000000020826
- [57] Aziz M, Bloomgarden N, Friedman N Primary aldosteronism presenting as chronic hypokalemia in a normotensive patient. *J Endocr Soc* 2022; 6: A256–A257. DOI: 10.1210/endo/bvac150.527
- [58] Mantero F, Terzolo M, Arnaldi G et al. A survey on adrenal incidentaloma in Italy. Study group on adrenal tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab* 2000; 85: 637–644. DOI: 10.1210/jcem.85.2.6372
- [59] Bernini G, Moretti A, Argenio G et al. Primary aldosteronism in normokalemic patients with adrenal incidentalomas. *Eur J Endocrinol* 2002; 146: 523–529. DOI: 10.1530/eje.0.1460523
- [60] Kim HY, Kim SG, Lee KW et al. Clinical study of adrenal incidentaloma in Korea. *Korean J Intern Med* 2005; 20: 303–309. DOI: 10.3904/kjim.2005.20.4.303
- [61] Comlekci A, Yener S, Ertilav S et al. Adrenal incidentaloma, clinical, metabolic, follow-up aspects: Single centre experience. *Endocr* 2010; 37: 40–46. DOI: 10.1007/s12020-009-9260-5
- [62] Kim J, Bae KH, Choi YK et al. Clinical characteristics for 348 patients with adrenal incidentaloma. *Endocrinol Metab (Seoul)* 2013; 28: 20–25. DOI: 10.3803/EnM.2013.28.1.20
- [63] Patrova J, Jarocka I, Wahrenberg H et al. Clinical outcomes in adrenal incidentaloma: Experience from one center. *Endocr Pract* 2015; 21: 870–877. DOI: 10.4158/EP15618.OR
- [64] Tabuchi Y, Otsuki M, Kasayama S et al. Clinical and endocrinological characteristics of adrenal incidentaloma in Osaka region, Japan. *Endocr J* 2016; 63: 29–35. DOI: 10.1507/endocrj.EJ15-0404
- [65] Stavropoulos K, Imprialos KP, Katsiki N et al. Primary aldosteronism in patients with adrenal incidentaloma: Is screening appropriate for everyone? *J Clin Hypertens (Greenwich)* 2018; 20: 942–948. DOI: 10.1111/jch.13291
- [66] Jing Y, Hu J, Luo R et al. Prevalence and characteristics of adrenal tumors in an unselected screening population: A cross-sectional study. *Ann Intern Med* 2022; 175: 1383–1391. DOI: 10.7326/M22-1619
- [67] Kmieć P, Zalewska E, Kunicka K et al. Autonomous aldosterone secretion in patients with adrenal incidentaloma. *Biomedicines* 2022; 10: 3075. DOI: 10.3390/biomedicines10123075
- [68] Fassnacht M, Arlt W, Bancos I et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2016; 175: G1–G34. DOI: 10.1530/EJE-16-0467
- [69] Lee J-M, Kim MK, Ko S-H et al. Clinical guidelines for the management of adrenal incidentaloma. *Endocrinol Metab (Seoul)* 2017; 32: 200–218. DOI: 10.3803/EnM.2017.32.2.200
- [70] Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71: 1269–1324. DOI: 10.1161/HYP.0000000000000066
- [71] Williams TA, Burrello J, Sechi LA et al. Computed tomography and adrenal venous sampling in the diagnosis of unilateral primary aldosteronism. *Hypertension* 2018; 72: 641–649. DOI: 10.1161/HYPERTENSIONAHA.118.11382

- [72] Sam D, Kline GA, So B et al. Discordance between imaging and adrenal vein sampling in primary aldosteronism irrespective of interpretation criteria. *J Clin Endocrinol Metab* 2019; 104: 1900–1906. DOI: 10.1210/jc.2018-02089
- [73] Wannachalee T, Caoili E, Nanba K et al. The concordance between imaging and adrenal vein sampling varies with aldosterone-driver somatic mutation. *J Clin Endocrinol Metab* 2020; 105: e3628–e3637. DOI: 10.1210/clinem/dgaa482
- [74] Nanba AT, Nanba K, Byrd JB et al. Discordance between imaging and immunohistochemistry in unilateral primary aldosteronism. *Clin Endocrinol (Oxf)* 2017; 87: 665–672. DOI: 10.1111/cen.13442
- [75] Omata K, Satoh F, Morimoto R et al. Cellular and genetic causes of idiopathic hyperaldosteronism. *Hypertension* 2018; 72: 874–880. DOI: 10.1161/HYPERTENSIONAHA.118.11086
- [76] Nishimoto K, Seki T, Hayashi Y et al. Human adrenocortical remodeling leading to aldosterone-producing cell cluster generation. *Int J Endocrinol* 2016; 2016: 7834356. DOI: 10.1155/2016/7834356
- [77] Piaditis GP, Kaltsas GA, Androulakis II et al. High prevalence of autonomous cortisol and aldosterone secretion from adrenal adenomas. *Clin Endocrinol (Oxf)* 2009; 71: 772–778. DOI: 10.1111/j.1365-2265.2009.03551.x
- [78] Markou A, Kaltsas GA, Papanastasiou L et al. Enhanced performance of a modified diagnostic test of primary aldosteronism in patients with adrenal adenomas. *Eur J Endocrinol* 2022; 186: 265–273. DOI: 10.1530/EJE-21-0625
- [79] Loh HH, Sukor N Primary aldosteronism and obstructive sleep apnea: What do we know thus far? *Front Endocrinol (Lausanne)* 2022; 13: 976979. DOI: 10.3389/fendo.2022.976979
- [80] Raff H, Roarty TP Renin, ACTH, and aldosterone during acute hypercapnia and hypoxia in conscious rats. *Am J Physiol* 1988; 254: R431–R435. DOI: 10.1152/ajpregu.1988.254.3.R431
- [81] Di Murro A, Petramala L, Cotesta D et al. Renin-angiotensin-aldosterone system in patients with sleep apnoea: Prevalence of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 2010; 11: 165–172. DOI: 10.1177/1470320310366581
- [82] Dobrowolski P, Kołodziejczyk-Kruk S, Warchoł-Celińska E et al. Primary aldosteronism is highly prevalent in patients with hypertension and moderate to severe obstructive sleep apnea. *J Clin Sleep Med* 2021; 17: 629–637. DOI: 10.5664/jcsm.8960
- [83] Buffolo F, Li Q, Monticone S et al. Primary aldosteronism and obstructive sleep apnea: A cross-sectional multi-ethnic study. *Hypertension* 2019; 74: 1532–1540. DOI: 10.1161/HYPERTENSIONAHA.119.13833
- [84] Kapur VK, Auckley DH, Chowdhuri S et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017; 13: 479–504. DOI: 10.5664/jcsm.6506
- [85] Chee MR, Hoo J, Libianto R et al. Prospective screening for primary aldosteronism in patients with suspected obstructive sleep apnea. *Hypertension* 2021; 77: 2094–2103. DOI: 10.1161/HYPERTENSIONAHA.120.16902
- [86] Chomsky-Higgins Menut K, Pearlstein SS, Conroy PC et al. Screening for primary aldosteronism in the hypertensive obstructive sleep apnea population is cost-saving. *Surgery* 2022; 171: 96–103. DOI: 10.1016/j.surg.2021.05.052
- [87] Rimoldi SF, Scherrer U, Messerli FH Secondary arterial hypertension: When, who, and how to screen? *Eur Heart J* 2014; 35: 1245–1254. DOI: 10.1093/eurheartj/ehf534
- [88] Viera AJ, Neutze DM Diagnosis of secondary hypertension: An age-based approach. *Am Fam Physician* 2010; 82: 1471–1478
- [89] Alam S, Kandasamy D, Goyal A et al. High prevalence and a long delay in the diagnosis of primary aldosteronism among patients with young-onset hypertension. *Clin Endocrinol (Oxf)* 2021; 94: 895–903. DOI: 10.1111/cen.14409
- [90] Nguyen V, Tu TM, Mamaug MJB et al. Primary aldosteronism more prevalent in patients with cardioembolic stroke and atrial fibrillation. *Front Endocrinol (Lausanne)* 2022; 13: 869980. DOI: 10.3389/fendo.2022.869980
- [91] Seccia TM, Letizia C, Muiesan ML et al. Atrial fibrillation as presenting sign of primary aldosteronism: Results of the Prospective Appraisal on the Prevalence of Primary Aldosteronism in Hypertensive (PAPPHY) Study. *J Hypertens* 2020; 38: 332–339. DOI: 10.1097/HJH.0000000000002250
- [92] McCarthy J, Yang J, Clissold B et al. Hypertension management in stroke prevention: Time to consider primary aldosteronism. *Stroke* 2021; 52: e626–e634. DOI: 10.1161/STROKEAHA.120.033990
- [93] Miyaji Y, Kawabata Y, Joki H et al. Primary aldosteronism in patients with acute stroke: Prevalence and diagnosis during initial hospitalization. *BMC Neurol* 2016; 16: 177. DOI: 10.1186/s12883-016-0701-5
- [94] Tyfoxylo E, Voulgaris N, Gravvanis C et al. High prevalence of primary aldosteronism in patients with type 2 diabetes mellitus and hypertension. *Biomedicines* 2022; 10: 2308. DOI: 10.3390/biomedicines10092308
- [95] Memon SS, Lila A, Barnabas R et al. Prevalence of primary aldosteronism in type 2 diabetes mellitus and hypertension: A prospective study from Western India. *Clin Endocrinol (Oxf)* 2022; 96: 539–548. DOI: 10.1111/cen.14598
- [96] Manosroi W, Atthakomol P High body fat percentage is associated with primary aldosteronism: A cross-sectional study. *BMC Endocr Disord* 2020; 20: 175. DOI: 10.1186/s12902-020-00654-w
- [97] Rossi GP, Rossi E, Pavan E et al. Screening for primary aldosteronism with a logistic multivariate discriminant analysis. *Clin Endocrinol (Oxf)* 1998; 49: 713–723. DOI: 10.1046/j.1365-2265.1998.00608.x