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REVIEW

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Who should be screened for primary aldosteronism? A comprehensive review of current evidence

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Abstract

Arterial hypertension is a major risk factor for cardiovascular disease. The prevalence of primary aldosteronism (PA) ranges from 5% to 10% in the general hypertensive population and is regarded as one of the most common causes of secondary hypertension. There are two major causes of PA: bilateral adrenal hyperplasia and aldosterone-producing adenoma. The diagnosis of PA comprises screening, confirmatory testing, and subtype differentiation. The Endocrine Society Practice Guidelines for the diagnosis and treatment of PA recommends screening of patients at an increased risk of PA. These categories include patients with stage 2 and 3 hypertension, drug-resistant hypertension, hypertensive with spontaneous or diuretic-induced hypokalemia, hypertension with adrenal incidentaloma, hypertensive with a family history of early onset

hypertension or cerebrovascular accident at a young age, and all hypertensive first-degree relatives of patients with PA. Recently, several studies have linked PA with obstructive sleep apnea and atrial fibrillation unexplained by structural heart defects and/or other conditions known to cause the arrhythmia, which may be partly responsible for the higher rates of cardiovascular and cerebrovascular accidents in patients with PA. The aim of this review is to discuss which patients should be screened for PA, focusing not only on well-established guidelines but also on additional groups of patients with a potentially higher prevalence of PA, as has been reported in recent research.

KEYWORDS
aldosterone renin ratio, hypertension, primary aldosteronism, screen

1 | INTRODUCTION

Arterial hypertension is a major risk factor of cardiovascular disease. It caused approximately 10.4 million deaths worldwide in 2016.[1,2] Over the past half-century, numerous studies have shown that effective blood pressure control reduces the risk of cardiovascular diseases, including coronary artery disease, stroke, and heart failure.[3,4] According to the hypertension recommendation published by Lancet,[3] many patients with poor blood pressure control have undiagnosed secondary hypertension. Primary hyperaldosteronism is one of the most common causes of secondary hypertension[5,6] and PA has been discovered for more than 60 years since Jerome Conn first reported this disease,[7] the prevalence of PA in the hypertensive population remains controversial. The prevalence depended on the population being examined,[8,9] and a recent systematic review reported the prevalence range from 3.2% to 12.7% in primary practice and from 1% to 30% in referral centers.[8] In particular, patients with PA have an increased risk of myocardial infarction, stroke, and arrhythmias.[10–12] Therefore, the confirmed diagnosis of PA is not only a very important step in leading to therapy but also helps clinicians to discern the exact impact on cardiovascular and cerebrovascular events[13] and metabolic complications[14] compared to patients with essential hypertension with a similar traditional risk profile.

The diagnosis of PA is a three-step process that comprises a screening test, confirmatory/exclusion test, and subtype differentiation (Figure 1), which has been summarized in the Taiwan Expert Consensus Document for PA,[15] 2020 TSOC/THS (TSOC: Taiwan Society of Cardiology/THS: Taiwan Hypertension Society) Home BP Consensus[16] and the 2022 Taiwan Hypertension Guideline.[17] Concerning the diagnostic process of PA, the current most reliable means of screening for PA is aldosterone renin ratio (ARR), which is superior to the measurements of both potassium and aldosterone (which are less sensitive), as well as renin alone (which is less specific).[18–20] Although the detailed diagnostic process has been addressed, the question: "who should be screened for PA?" is still controversial. In 2020, the European Society of Endocrinology and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension[21] provided screening recommendations for clinicians in clinical practice and challenged the 2016 Endocrine Society Practice Guideline,[22] which provides clinicians with the best available research evidence in the field and significantly contributes to improve the quality of care. With evolving evidence and guideline, the present review comprehensively examined the current evidence and provide a summary on who should be screened for PA. Recently, a positive relationship between hyperaldosteronism and the severity of obstructive sleep apnea (OSA) has been reported, and a high likelihood of coexisting hyperaldosteronism has been noted in patients with resistant hypertension (RH).[23] Therefore, we also provide the new evidence pertaining to the relationship of PA with atrial fibrillation and OSA in this review.

1.1 | Candidates are screened for PA based on guidelines and consensus

Depending on comprehensive review of the prevalence of PA (Table 1 and 2),[15,21,22,24,25] we listed candidates for PA screening suggested as follows, based on three guidelines and consensus.

1. Patients with stage 2 and stage 3 hypertension
2. Patients 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 (drug-resistant hypertension, RH)
3. Hypertension and spontaneous or diuretic-induced hypokalemia
4. Hypertension and adrenal incidentaloma
5. Hypertension and obstructive sleep apnea
6. Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years)
7. Hypertensive first-degree relatives of patients with PA.
8. Atrial fibrillation unexplained by structural heart defects and/or other conditions known to cause the arrhythmia

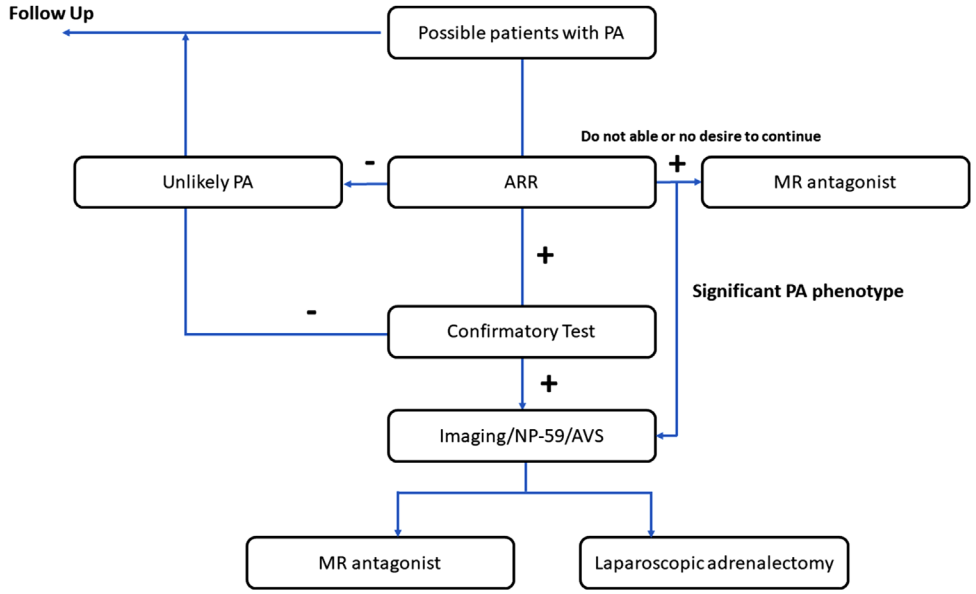

FIGURE 1 The flow chart of diagnosis of PA in the Taiwan Expert Consensus Document for Primary aldosteronism.[15] ARR, Aldosterone Renin Ratio; AVS, Adrenal Vein Sampling; PA, Primary Aldosteronism; MR, mineralocorticoid receptor; NP-59, iodine-131-beta-iodomethyl-nocholesterol

TABLE 1 The prevalence of primary aldosteronism (PA) (modified from 2016 European Society Practice Guidelines for diagnosis and treatment of PA[22])

Patient group	Prevalence
Moderate/severe hypertension: ✓ The prevalence rates are from Mosso and coworkers[70] and others have reported similar estimates[71–74] listed in table 2. ✓ The classification of BP for adults (aged > 18 years) was based on the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[75] ✓ The three stages of hypertension: A. Stage 1 = SBP 140–159 mm Hg, DBP 90–99 mm Hg B. Stage 2 = SBP 160–179 mm Hg, DBP 100–109 mm Hg C. Stage 3 = SBP > 180 mm Hg, DBP ≧110 mm Hg[76] **D**. If SBP and DBP were in different categories, the higher category was selected for classification.	Overall prevalence: 6.1% Stage 1 (mild): 2% Stage 2 (moderate): 8% Stage 3 (severe): 13%
Resistant hypertension ✓ SBP > 140 mm Hg and DBP > 90 mm Hg despite treatment with three hypertensive medications[29,32,77–79]	The prevalence of PA is often positively correlated with severity of hypertension and the reports showed 17%–23%.
Hypertensive patients with spontaneous or diuretic-induced hypokalemia.	The prevalence of PA in patients with hypertension and serum K < 3.7 mmol/l is 28.1% and rises up to 88.5% in patients with spontaneous hypokalemia of less than 2.5 mmol/l.[37]
Hypertension with adrenal incidentaloma[80–85] ✓ An adrenal mass detected incidentally during imaging performed for extra-adrenal reasons.	Median, 2% (range, 1.1%–10%).
Hypertension with obstructive sleep apnea[60,67]	34% among newly hypertensive patients with obstructive sleep apnea.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2 The detailed prevalence of PA in hypertensive patients (modified from Nishikawa Study[25])

Author (year)	Patients	Screening test	Confirmatory test for diagnostic examination	Prevalence of PA
Gordon and coworkers[86] (1994)	199 hypertensive patients	ARR > 30 seated for 5 min medication was continued	FST	8.5%
Komiya and coworkers[87] (1996)	741 hypertensive patients			4.2%
Lim and coworkers[88] (2000)	495 hypertensive patients	ARR > 27 sitting for 10 min medication was stopped	FST and salt loading test	9.2%
Fardella and coworkers[76] (2000)	305 hypertensive patients	ARR > 50 and PAC > 16 ng/dl sitting for 15 min	FST	9.5%
Loh and coworkers[89] (2000)	350 hypertensive patients	ARR > 20 and PAC > 15 ng/dl seated for 15 min medication was continued	Salt loading test	4.6%
Rossi and coworkers[73] (2002)	1065 hypertensive patients	Post-captopril ARR > 35 seated for 90 min	Salt loading test	6.3%
Strauch and coworkers[74] (2003)	402 patients	ARR > 50		19%
Mulatero and coworkers[90] (2004)				
Mulatero and coworkers	7343 hypertensive patients	ARR > 40 and PAC > 15 ng/dl	Salt loading test	8%
Young and coworkers	1112 hypertensives	ARR > 20 and PAC > 15 ng/dl	Salt loading test	10.8%
Stowesser and coworkers		ARR > 30	FST	21.7%
Loh and coworkers	3850 patients	ARR > 20	Salt loading test	4.6%
Nishikawa & Omura[25] (2000) ; Omura and coworkers[91] (2004)	1020 hypertensives patients	PAC > 12 ng/dl and PRA < 1.0 ng/ml/h rested in spine position for 30 min without medication	ACTH-AVS	5.4%–6%
Williams and coworkers[72] (2006)	346 patients	ARR > 25 and PAC > 8 ng/dl	Urinary aldosterone excretion	3.2%
Mosso and coworkers[70] (2003)	609 hypertensive patients	ARR > 25	FST	6.1%
Hannemann[71] and coworkers (2012)	280 patients			7%

Abbreviations: ARR, aldosterone-renin ratio; FST, fludrocortisone-suppression test; PAC, plasma aldosterone concentration; PRA, plasma rennin activity.

2 | PREVALENCE AND SCREENING OF SUBGROUPS OF HYPERTENSIVE PATIENTS

2.1 | Prevalence of PA in patients with hypertension stage 2 and stage 3 and drug-resistant hypertension

PA prevalence varies according to the degree of hypertension. Mosso and coworkers[26] study and 2016 Endocrine Society practice guideline[22] revealed a prevalence of 2% in stage 1 hypertension, 8% in stage 2, and 13% in stage 3, while another study performed in Italy reported a PA prevalence of 6.6%, 15.5%, and 19% in stage 1, 2, and 3 hypertension, respectively.[27] Therefore, these studies provided information that the probability of having PA is positively associated with the severity of hypertension. RH is defined as the prescription of at least three drugs (including a diuretic) in adequate doses that have failed to lower the blood pressure to the desired level or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs.[16,17,28] The PA prevalence in patients with RH ranged from 14%–23%.[29–33] Because of the failure in treating resistant hypertension, PA identification and subsequent adrenalectomy are recommended as important procedures to control blood pressure levels in patients who might need lifelong therapy with multidrug regimens. Therefore, screening can often be restricted to hypertensive subgroups with a higher prevalence to avoids false-positive results and a large increase in costs. Hung and coworkers also stated that the population characteristics, ARR diagnostic threshold, laboratory assay, and reference standard for confirmatory testing varied substantially between the enrolled studies in their meta-analysis.[34] The reported ARR sensitivity and specificity varied widely, with sensitivity ranging from 10% to 100% and specificity ranging from 70% to 100%. Therefore, this study suggests that the limitations in the accuracy and reliability of ARR must be recognized for an appropriate clinical decision-making. Furthermore, a cost-effectiveness study conducted in Japan by Sato and coworkers[35] suggested comprehensive screening of all patients with hypertension for primary hyperaldosteronism. In this study, the cost of comprehensive screening was reported to be 64 004 yen, but it only extended .013 years in expected life. However, because of the related unnecessary costs in different healthcare systems, a comprehensive screening strategy for PA in different countries should consider the inaccuracy of ARR for PA. Therefore, in the absence of more precise diagnostic tools and sufficient evidence to support

TABLE 3 Recommendations for primary aldosteronism (PA) screening in different categories of patients

Subgroup	2022 Taiwan Expert Consensus Document for Primary aldosteronism	2016 European Society of Endocrinology Guideline[22]	2020 Working Group on Endocrine Hypertension of the European Society of Hypertension[21]	Evidence
Groups indicated by guidelines				
Patients with hypertension Stage 2 and 3	1C	1C	recommendation	**15-17,21-22, 26–33,70-79**
Drug-resistant hypertensives	1C	1C	recommendation	**15-17,21-22, 26–33,70-79**
Hypertensives with spontaneous or diuretic-induced hypokalemia	1C	1C	recommendation	**7,27,36-37**
Hypertensives with adrenal incidentaloma	2C	1C	recommendation	**22,24,38-40,80-85**
Hypertensives with a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years)	1C	1C	recommendation	**5,18,41-56**
All hypertensives first-degree relatives of patients with PA	2C	1C	recommendation	**5,18,41-56**
Other groups with high PA prevalence				
Hypertensives with obstructive sleep apnea (OSA)	2C	1C	suggestion	**21-23,57-67**
Groups in which indication is still debated or not suggested				
All hypertensives Stage 1	Expert Opinion	Expert Opinion	Expert Opinion	**15-17,21-22**
Pre-hypertensives	Expert Opinion	Expert Opinion	Expert Opinion	**15-17,21-22**
Hypertensives with atrial fibrillation unexplained by structural heart defects	2D	2C	recommendation	**65-66**

comprehensive screening, we adopted the same criteria as international guidelines[15,21,22]: screening for primary hyperaldosteronism in certain groups of diseases, and not in the general hypertensive population (Table 3).

2.2 | Hypertension and spontaneous or diuretic-induced hypokalemia

Since J. W. Conn first described it in 1955, hypokalemia was thought to be a crucial clinical manifestation of PA.[7] Current data from a nationwide registry of hypertensive report a prevalence of hypokalemia of only 3.8%.[36] Hypokalemia, either spontaneously developed or diuretic-induced, is much more common in patients with PA than in those with essential hypertension. The prevalence of hypokalemia has been reported to be different among PA subtypes; nearly half of the patients with APA and only 17% of those with bilateral adrenal hyperplasia (BAH) were observed to have hypokalemia.[27] Hypokalemia is currently defined as serum potassium below 3.5 mmol/L, by definition; however, there are some patients with serum potassium between 3.5 mmol/L and 3.8 mmol/L. Burrello and coworkers[37] conducted an observational study of 5100 hypertensive patients, investigating the prevalence of hypokalemia in PA. They showed that the prevalence of PA increased with decreasing serum potassium level (5.2 mmol/L to < 2.5 mmol/L; Figure 2). In this study of 5100 patients with hypertension, 15.8% enrolled patients had hypokalemia, 76.9% had normal potassium level, and 7.3% had hyperkalemia. The prevalence of PA in patients with hypokalemia was 28.1%, and 57.1% PA patients had hypokalemia. It was also found that the prevalence of primary hyperaldosteronism increased to 88.5% in study patients with spontaneous hypokalemia and serum potassium concentrations below 2.5 mmol/L. In summary, PA is a frequent cause of secondary hypertension in patients with hypokalemia, and the presence of hypertension and spontaneous hypokalemia are strong indications for PA screening and diagnosis.

2.3 | Hypertension with adrenal incidentaloma

The prevalence of adrenal incidentaloma was reported as approximately 6% in autopsy studies and 4.33% in China.[38] However, it is an age-related condition. The prevalence in patients below 30 years of age was less than 1% and in those who were older than 70 years of age was 7%.[39] It is estimated that the prevalence of PA among patients with adrenal incidentaloma is approximately 2%.[22,24] To determine whether the adrenal incidentaloma is associated with excess secretion of

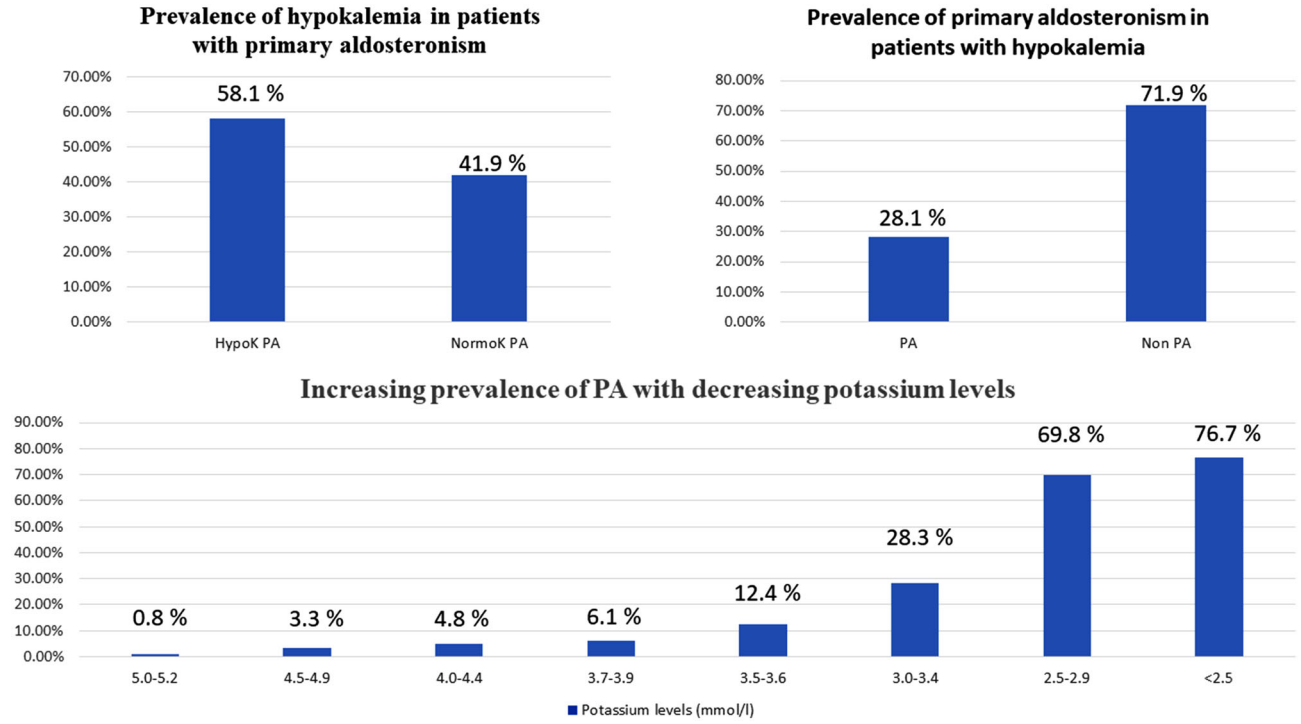

FIGURE 2 Hypokalemia and primary aldosteronism in hypertensive patients (modified from Burrello study).[37] NormoK, normokalemia; HypoK, Hypokalemia; PA, primary aldosteronism

aldosterone, screening should be considered in patients with hypertension having adrenal incidentaloma.[40]

2.4 | Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (< 40 years); all hypertensive first-degree relatives of patients with PA

Based on the evidence from genetic studies, four forms of familial hyperaldosteronism (FH) have been described: type I (or glucocorticoid-remediable aldosteronism [GRA]), type II, type III and type IV. FH has also been reported as a rare cause of PA. The study of FH was a useful approach to understand the pathophysiology of PA due to its heritability. Some causative genes, including *CYP11B1* (FH 1),[41] *CYP11B2* (FH 1),[41] *CLCN2* (FH 2),[42] *KCNJ5* (FH 3),[43] *and CACNA1H* (FH 4)[44] have been identified in FH. FH-I is the most common form of monogenic hypertension that accounts for less than 1% of all PA cases.[45] Because of the recombination of *CYP11B1* and *CYP11B2*, FH-1 produces a chimeric enzyme, which is often located in the zona fasciculata-reticularis, resulting in aldosterone production under the control of adrenocorticotropic hormone rather than angiotensin II.[41] The clinical features of GRA are variable and characterized by an early onset of hypertension.[46] Litchfield conducted a retrospective analysis of 367 patients with GRA, and the results revealed that patients with FH-I/GRA displayed higher morbidity and mortality from cerebrovascular events than those without GRA.[47] FH type II (FH-II) is a non-glucocorticoid-remediable form of PA that is clinically and biochemically different from sporadic PA.[18,48] FH-II is an early onset form of primary aldosteronism caused by germline mutations in the CLCN2 gene.[42,49] In clinical practice, we often suspect patients with FH-II based on at least two first-degree members of the same family with confirmed PA without the hybrid gene mutation of FH-1/GRA.[18] A FH-III is characterized by a particularly severe form of hyperaldosteronism resistant to aggressive pharmacotherapy, thus requiring bilateral adrenalectomy[50,51] and is often associated with mutations in the gene encoding the potassium channel *KCNJ5*.[43,52,53] Finally, FH-IV is a rare disorder and caused by germline mutations in the CACNA1H gene.[44]

Secondary hypertension was more frequently observed in children than in adults, but endocrine hypertension is not regarded as a common cause.[54] The median age at the diagnosis of primary hyperaldosteronism is nearly 50 years.[5,55] Therefore, younger patients might benefit more from treatment for primary aldosteronism. The benefit of screening for young patients at an early stage of primary aldosteronism could result in an increased quality of life and a better cardiovascular outcome.[56] Therefore, we recommend that all young hypertensive patients should be screened for PA even without familial history. Early screening will result in a better cardiovascular protection for young hypertensive patients.[5,55]

2.5 | Patients with obstructive sleep apnea

OSA is strongly associated with the risk of hypertension,[57,58] and the severity of hypertension is associated with an increased risk of

OSA.[59] Calhoun and coworkers reported increased aldosterone excretion in patients with RH and worsening symptoms of OSA. As such, the 2016 Endocrine Society Practice Guideline also suggested screening for PA in OSA patients.[22] However, a previous small single-center study reported a similar prevalence of 34% in 53 patients with sleep apnea.[60] A recent multicenter study (HYPNOS study),[61] conducted by Mulatero and coworkers, challenged the current recommendation of the 2016 Endocrine Society guideline. In HYPNOS study, the prevalence of PA in patients with OSA and requiring CPAP treatment was 8.9%, a figure not significantly different either from the 5.9% observed in the general hypertensive population of the Primary aldosteronism in Torino study[5] or from the 11.2% of the referred patients from the Primary aldosteronism prevalence in hypertensives study.[61] Subsequently, Mulatero and coworkers on behalf of working group of the European Society of Hypertension investigators reported the consensus[21] and they suggested, rather recommended, screening for PA in patients with OSA.

Regarding the association between OSA and PA, several points are worthy of considerations. First, increased aldosterone level has an impact on blood pressure and fluid homeostasis. The earlier studies assessing OSA severity[23] and aldosterone excess demonstrated clearly the effect of continuous positive airway pressure treatment on aldosterone level,[62,63] which provides the pathophysiological linkage between OSA and hypertension. Second, in HYPNOS study, the AHI was derived from cardiorespiratory polygraphy.[64] Notably, polygraphy-derived Apnea-Hypopnea Index (AHI) is ≈30% lower than AHI calculated by polysomnography. Lastly, the Endocrine Society guidelines issued in 2016 extended recommendations for PA screening not only to OSA hypertensive patients but also favored PA screening in newly diagnosed hypertensive patients with BP values exceeding 150/100 mm Hg, which is commonly observed in newly diagnosed hypertensive patients with OSA. Taking the body of evidence into consideration, we suggest that screening for PA in patients with OSA may be considered.

2.6 | Patients with atrial fibrillation

Monticone[65] and coworkers conducted a meta-analysis and reported that atrial fibrillation is often considered an important complication in PA patients. This study included seven review papers with a total of 6580 patients. The results revealed that patients with PA were at least 3.52 times more likely to have atrial fibrillation than those with essential hypertension. Thus, we should screen for PA in patients with hypertension and atrial fibrillation unexplained by structural heart defects and/or other conditions known to cause the arrhythmia.[66]

2.7 | Other conditions that warrant screening for PA

Primary aldosteronism plays an important role in conditions with obesity-associated risk factor, such as metabolic syndrome and diabetes mellitus.[67] Several studies had revealed a higher prevalence of metabolic syndrome and insulin resistance/type 2 diabetes mellitus in patients with primary aldosteronism.[68,69] However, further studies are required to evaluate detailed mechanisms. There are certain groups in which indications for PA screening still debated or not suggested, including all patients with prehypertension and hypertension stage I or patients with hypertension and having atrial fibrillation. The screening of all patients with hypertension will lead to increase in false-positives and a large increase in costs. Thus, screening should be restricted to groups with higher prevalence of PA in order to appropriately inform clinical decision-making.

3 | SUMMARY AND CONCLUSIONS

PA is a common cause of secondary hypertension and is often associated with an increased risk of cardiovascular events including left ventricular hypertrophy, arrhythmia, and myocardial infarction. Therefore, all patients with hypertension with an increased possibility of this disease should be carefully screened to confirm the diagnosis or exclude hyperaldosteronism. The 2016 Guidelines of the Endocrine Society and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension defined the different categories of patients that should be screened for PA. Given the experimental and epidemiological evidence, patients must be screened for this disease aggressively in clinical practice. Patients with RH, patients with stage 2 and stage 3 hypertension, hypertensives with a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years), all hypertensive first-degree relatives of patients with PA, hypertensive with spontaneous or diuretic-induced hypokalemia, hypertensive patients with OSA or atrial fibrillation unexplained by structural heart defects and/or other conditions known to cause the arrhythmia are also strong candidates to be considered in the screening for PA.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DISCLOSURE

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