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

Wei-Chieh Huang MD1,2  |  Yen-Hung Lin MD, PhD3,4  |  Vin-Cent Wu MD, PhD3,4  |  Chen-Huan Chen MD5  |  Saulat Siddique MBBS, MRCP (UK), FRCP (Lon)6  |  Yook-Chin Chia MBBS, FRCP7,8  |  Jam Chin Tay MBBS, FAMS9  |  Guruprasad Sogunuru MD, DM, FISC, FIAMS, FESC10  |  Hao-Min Cheng MD, PhD11,12,13,14  |  Kazuomi Kario MD, PhD15

1 Division of Cardiology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan  
2 School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan  
3 Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan  
4 Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University Hospital, Taipei, Taiwan  
5 Department of Internal Medicine, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan  
6 Punjab Medical Center, Lahore, Pakistan  
7 Department of Medical Sciences, School of Medical and Life Sciences, Sunway University, Bandar Sunway, Malaysia  
8 Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia  
9 Department of General Medicine, Tan Tock Seng Hospital, Singapore, Singapore  
10 Department of Cardiology, College of Medical Sciences, Kathmandu University, Kathmandu, Nepal  
11 Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan  
12 Ph.D. Program of Interdisciplinary Medicine (PIM), National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan  
13 Institute of Public Health, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan  
14 Institute of Health and Welfare Policy, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan  
15 Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

Correspondence  
Hao-Ming Cheng MD, PhD, No. 201, Sec. 2, Shih-Pai Road, Beitou District, Taipei 111, Taiwan, ROC.  
Email: hmcheng@vghtpe.gov.tw

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,5 many patients with poor blood pressure control have undiagnosed secondary hypertension. Primary hyperaldosteronism is one of the most common causes of secondary hypertension5,6 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.10 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 events13 and metabolic complications14 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 Consensus16 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 Hypertension21 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.\textsuperscript{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\textsuperscript{22})

| Patient group                                           | Prevalence                     |
|---------------------------------------------------------|--------------------------------|
| Moderate/severe hypertension:                          | Overall prevalence: 6.1%        |
| ✓ The prevalence rates are from Mosso and coworkers\textsuperscript{70} and others have reported similar estimates\textsuperscript{71–74} listed in table 2. | Stage 1 (mild): 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.\textsuperscript{75} | Stage 2 (moderate): 8%         |
| ✓ The three stages of hypertension:                    | Stage 3 (severe): 13%          |
| 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 \(\geq\) 110 mm Hg\textsuperscript{76} |                                |
| D. If SBP and DBP were in different categories, the higher category was selected for classification. |                                |
| Resistant hypertension                                  | The prevalence of PA is often positively correlated with severity of hypertension and the reports showed 17%–23%.|
| ✓ SBP > 140 mm Hg and DBP > 90 mm Hg despite treatment with three hypertensive medications\textsuperscript{29,32,77–79} |                                |
| 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\textsuperscript{37} |
| Hypertension with adrenal incidentaloma\textsuperscript{60–85} | Median, 2% (range, 1.1%–10%). |
| ✓ An adrenal mass detected incidentally during imaging performed for extra-adrenal reasons. |                                |
| Hypertension with obstructive sleep apnea\textsuperscript{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\textsuperscript{25})

| Author (year) | Patients | Screening test | Confirmatory test for diagnostic examination | Prevalence of PA |
|---------------|----------|----------------|---------------------------------------------|------------------|
| Gordon and coworkers\textsuperscript{86} (1994) | 199 hypertensive patients | ARR > 30 seated for 5 min medication was continued | FST | 8.5% |
| Komiya and coworkers\textsuperscript{87} (1996) | 741 hypertensive patients | | | 4.2% |
| Lim and coworkers\textsuperscript{88} (2000) | 495 hypertensive patients | ARR > 27 sitting for 10 min medication was stopped | FST and salt loading test | 9.2% |
| Fardella and coworkers\textsuperscript{76} (2000) | 305 hypertensive patients | ARR > 50 and PAC > 16 ng/dl sitting for 15 min | FST | 9.5% |
| Loh and coworkers\textsuperscript{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\textsuperscript{73} (2002) | 1065 hypertensive patients | Post-captopril ARR > 35 seated for 90 min | Salt loading test | 6.3% |
| Strauch and coworkers\textsuperscript{74} (2003) | 402 patients | ARR > 50 | | 19% |
| Mulatero and coworkers\textsuperscript{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\textsuperscript{25} (2000) ; Omura and coworkers\textsuperscript{91} (2004) | 1020 hypertensive 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\textsuperscript{72} (2006) | 346 patients | ARR > 25 and PAC > 8 ng/dl | Urinary aldosterone excretion | 3.2% |
| Mosso and coworkers\textsuperscript{70} (2003) | 609 hypertensive patients | ARR > 25 | FST | 6.1% |
| Hannemann\textsuperscript{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\textsuperscript{26} study and 2016 Endocrine Society practice guideline\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,17,28} The PA prevalence in patients with RH ranged from 14%–23%.\textsuperscript{29–32} 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.\textsuperscript{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\textsuperscript{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 Guideline22 | 2020 Working Group on Endocrine Hypertension of the European Society of Hypertension21 | 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 guidelines15,21,22: 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 coworkers27 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
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), CYP11B2 (FH 1), CLCN2 (FH 2), KCNJ5 (FH 3), and CACNA1H (FH 4) 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. 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. The clinical features of GRA are variable and characterized by an early onset of hypertension. 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. FH type II (FH-II) is a non-glucocorticoid-remediable form of PA that is clinically and biochemically different from sporadic PA. FH-II is an early onset form of primary aldosteronism caused by germline mutations in the CLCN2 gene. 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. A FH-III is characterized by a particularly severe form of hyperaldosteronism resistant to aggressive pharmacotherapy, thus requiring bilateral adrenalectomy and is often associated with mutations in the gene encoding the potassium channel KCNJ5. Finally, FH-IV is a rare disorder and caused by germline mutations in the CACNA1H gene.

Secondary hypertension was more frequently observed in children than in adults, but endocrine hypertension is not regarded as a common cause. The median age at the diagnosis of primary hyperaldosteronism is nearly 50 years. 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. 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.

Patients with obstructive sleep apnea

OSA is strongly associated with the risk of hypertension 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 study5 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 consensus21 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 severity23 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

Monticone65 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 dia-

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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ORCID

Saulat Siddique MBBS, MRCP (UK), FRCP (Lon) https://orcid.org/0000-0003-1294-0430
Jam Chin Tay MBBS, FAMS https://orcid.org/0000-0001-7657-4383
Guruprasad Segunuru MD, DM, FISC, FIAMS, FESC https://orcid.org/0000-0002-1410-9328
Hao-Min Cheng MD, PhD https://orcid.org/0000-0002-3885-6600
Kazuomi Kario MD, PhD https://orcid.org/0000-0002-8251-4480

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