Improving Detection Rates for Primary Aldosteronism

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ABSTRACT

Primary aldosteronism (PA), once considered a rare disease, is being increasingly recognized as an important cause of hypertension. It is associated with higher rates of cardiovascular complications compared to blood pressure-matched essential hypertension. Targeted treatments are available which can mitigate the excess cardiovascular risks and, in some cases, cure hypertension. Making a timely diagnosis of PA is, therefore, highly beneficial for patients. Furthermore, numerous studies from different parts of the world have found PA to be a relatively common disease that can affect patients in any stage of hypertension, regardless of their age or potassium levels. Despite this well-established data, the current rate of PA detection is appallingly low, much below its actual prevalence. This review explores the challenges that clinicians often face in diagnosing PA and offers strategies that may improve the detection of this potentially curable form of hypertension.

Introduction

Primary aldosteronism (PA), a condition characterized by autonomous aldosterone secretion by the adrenal gland(s), is increasingly recognized as an important secondary cause of hypertension [1]. Compared with blood pressure-matched essential hypertension, patients with PA are at increased risk of cardiovascular events including stroke, coronary artery disease, heart failure, and atrial fibrillation [2–4]. Treatment with unilateral adrenalectomy or a mineralocorticoid receptor (MR) antagonist can mitigate many of these cardiovascular complications, especially if started early in the course of the disease [5–7]. Thus, it is important to diagnose PA on time.

The United States Endocrine Society recommends PA screening for specific groups of patients including those with severe hypertension, resistant hypertension, or hypertension with hypokalaemia [1]. Screening is generally performed by measuring the plasma aldosterone-to-renin ratio (ARR) [1]. In PA, the aldosterone level is normal or elevated, but the level of renin is suppressed, leading to an elevated ARR. An abnormal result in the screening test is generally followed by confirmatory testing such as saline suppression, oral salt loading, or fludrocortisone suppression testing. Although PA screening is recommended in patients with the high-risk features described above, in reality very few of these patients are tested [8, 9]. Despite the dire consequences of untreated PA and the availability of effective treatment options, PA remains substantially under-appreciated [10]. This review discusses the gap between the prevalence of PA and current detection rates, identify barriers to diagnosis, and discuss possible strategies to improve its detection.

Primary aldosteronism is not a rare disease

First described by Conn in 1955, PA was traditionally considered a rare disease manifesting with resistant hypertension and severe hypokalaemia [11]. However, over the past three decades, substan-

tial evidence has emerged showing that PA is more common than initially thought. Studies conducted in the primary care setting with the aim of actively looking for PA have reported a prevalence of 3 to 14 % (▶ **Table 1**) [12–26]. The prevalence estimates vary depending on the diagnostic threshold used to define PA, with more stringent thresholds unsurprisingly associated with a lower prevalence [27]. Unfortunately, there are no internationally standardized criteria for the diagnosis of PA. While unilateral PA can be confirmed following a surgical cure, there is no gold standard for the diagnosis of PA caused by bilateral adrenal disease [10]. Setting a specific diagnostic threshold following dynamic testing may be complicated by the continuum of renin-independent aldosteronism that occurs in PA [28]. Indeed, there have been calls to widen the inclusion criteria for PA to reflect this continuum, which would push the prevalence even higher [29,30].

The prevalence of PA is highest in specialist clinics and tertiary centers where the value reaches 30 % [31]. Certain groups of patients have a higher risk of developing PA. In patients with resistant hypertension, defined as uncontrolled blood pressure despite treatment with at least three antihypertensive medications including a diuretic, PA was found in 29 % of cases [32]. In the PATHWAY-2 randomized controlled trial which compared several medications to treat resistant hypertension, the MR antagonist spironolactone led to the greatest reduction in blood pressure leading the authors to estimate that up to 38 % of the participants in this trial may have had undiagnosed PA [33, 34]. In another study on 256 patients with new-onset type 2 diabetes and hypertension, 19 % were diagnosed with PA [35]. PA is also common in patients with atrial fibrillation without a known cause for the arrhythmia. For example, a study showed that in this group, PA was found in 42 % and half of them had the surgically curable form of PA [36].

An important finding that arose from these studies was that most patients with PA were in fact normokalaemic [12, 13]. Only 17-30 % of PA patients had hypokalaemia with a higher rate of hypokalaemia observed in patients with unilateral, compared with bilateral, PA (50 % vs. 20 % in the respective groups) [12, 13]. Furthermore, these studies demonstrated that PA affects not only patients with resistant or severe hypertension, but also those with early-stage hypertension [30]. Using 24 h urinary aldosterone measurements, Brown et al. (2020) reported that the prevalence of PA was 16 % in patients with stage 1 hypertension and 22 % in patients with resistant hypertension [30]. Further, even in people with untreated hypertension, a prevalence of up to 14 % had been reported [14]. Thus, PA is a relatively common disease in both primary and tertiary care settings. Furthermore, patients with PA may have a varied presentation and are not confined to the typical features of resistant hypertension and hypokalaemia.

The current detection rate of primary aldosteronism is very low

Despite being relatively common, in real life, PA is rarely detected. Studies from different parts of the world have shown that PA detection in the community is much below its prevalence rate. In a survey of 500 General Practitioners (GPs) (250 in Italy and 250 in Germany), only 1-2 % of hypertensive patients managed by these GPs had a diagnosis of PA [37]. In another study from Italy, over a 16-year period, only 992 patients were discharged from hospitals across the Emilia-Romagna region with discharge coding consistent with PA as per the International Classification of Diseases 9 Clinical Modification code [38]. With an estimated actual PA prevalence of 5% based on epidemiological studies, this figure corresponds to only 2 % of all expected cases of PA being diagnosed during that time [38]. A similar finding was reported in Australia; in a dataset collected from over 15,000 Australian GPs over 16 years, there were only 57 cases of PA among 1.5 million patient-GP interactions [39]. The low detection rate is reflected in the under-utilization of ARR measurement as a screening tool for PA [1]. In the European study reported above, only 7 % of GPs had ever recommended renin and aldosterone measurements [37]. Among 1.1 million adults with hypertension in Canada, less than 1 % were ever screened for PA [40]. Further, in the Australian GP dataset, an aldosterone measurement was only documented 66 times over 16 years [39].

Such low detection rates of PA were also seen in selected groups of patients despite the presence of characteristics traditionally associated with PA. Among 269,000 US veterans with resistant hypertension for whom guidelines suggest that PA should be tested for, only 1.6 % were actually tested [9]. Of the 4277 individuals who were tested in this cohort, 12 % had evidence of PA on initial testing [9]. Even among patients with hypertension and hypokalaemia, a very small minority were tested for PA. For example, Hundemer et al. (2022) performed a retrospective cohort study of > 26,000 adults in Ontario, Canada with hypertension and hypokalaemia and found only 422 underwent PA screening [8]. Among individuals with severe hypokalaemia (serum potassium below 3 mmol/L), only 4 % were screened [8]. This study did not report the number of PA cases diagnosed following screening.

Similarly, low records of PA testing have been reported in specialist clinics. In a retrospective study of diabetes patients seen in a tertiary center, 23 % had indications for PA screening according to the Endocrine Society recommendations but only 6 % were screened [41]. In nephrology clinics, though 39 % of the patients had an indication for PA screening, again, only 6 % were tested [42]. By the time hypertensive patients were referred for further investigations and found to have PA, 40 % had developed end-organ damage [43]. These studies highlighted diagnostic inertia as a global issue facing patients with PA who are not diagnosed or received a late diagnosis.

Challenges in the diagnosis of primary aldosteronism

An understanding of the current challenges in diagnosing PA is needed to effect changes and improve its detection (▶ **Fig. 1**). Few studies have been performed to primarily address this question, but they provided important insights. In one study, Jaffe et al. (2022) sought to determine the factors associated with PA screening among patients with resistant hypertension within an academic health system [44]. They found that screening was more likely to be performed in patients who were younger, more hypertensive, and had a lower serum potassium level [44]. Conversely, patients with significant co-morbidities were less likely to be screened. This study highlighted two important challenges in diagnosing PA: first, clinicians were more likely to screen patients who fit the traditional picture of PA. The research that demonstrates the lack of unique clinical features which differentiate PA from other forms of hypertension has perhaps not been adequately disseminated to influence

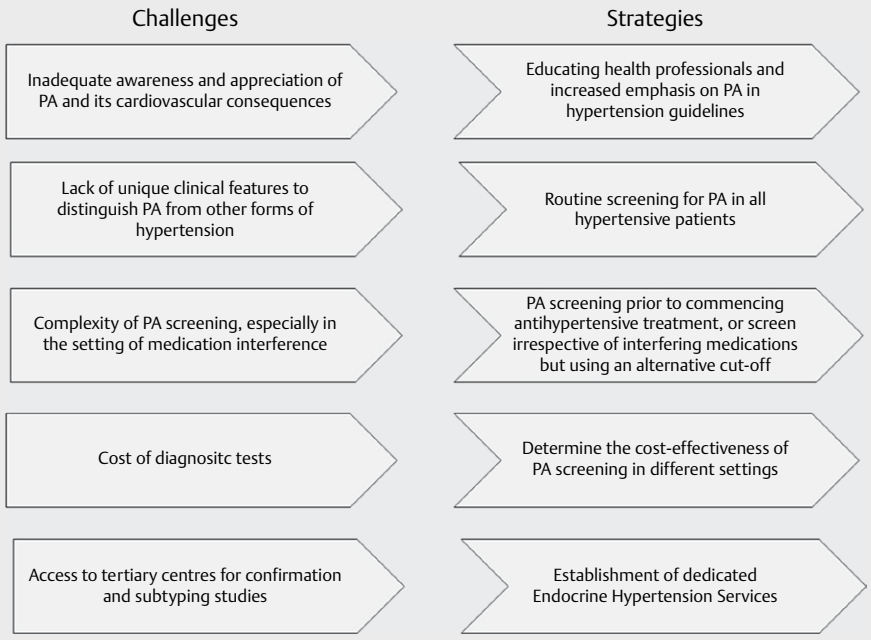
▶ **Table 1** Prevalence of PA in primary care based on studies published in the past 30 years.

Author, year of publication (ref)	Country	Population	Diagnostic criteria	Prevalence of confirmed PA
Libianto et al., 2022 (14)	Australia	247 patients with treatment naïve HT from 31 GP practices	*Screening:* ARR > 70 pmol/mU *Confirmation:* PAC > 140 pmol/L post recumbent SST or > 170 pmol/L post seated SST	14 %
Xu et a,l, 2020 (13)	China	1402 patients with HT from a large community health center	*Screening:* ARR > 55 pmol/mU and PAC > 280 pmol/L *Confirmation:* PAC > 280 pmol/L post CCT, or > 180 pmol/L post seated SST	4 %
Kayser et al., 2018 (16)	Netherlands	343 patients with newly diagnosed (untreated) HT	*Screening:* ARR > 40 pmol/mU and PAC > 400 pmol/L *Confirmation:* PAC > 280 pmol/L post SST	2.6 %
Monticone et al., 2017 (12)	Italy	1672 consecutive patients with HT presenting to 19 GPs	*Screening:* ARR > 100 pmol/mU and PAC > 277 pmol/L *Confirmation:* PAC > 140 pmol/L post SST, or ARR > 100 pmol/mU post CCT	5.9 %
Galati et al., 2016 (17)	US	296 patients with HT from the primary care clinic of Mt Sinai Hospital	*Screening:* ARR > 70 pmol/mU and PAC > 280 pmol/L and PRA < 1 ng/mL/h *Confirmation:* urine aldosterone > 12 mmol/L post oral salt loading	0.7 %
Volpe et al., 2013 (18)	Sweden	182 patients with HT from one GP practice	*Screening:* ARR > 30 pmol/mU and PAC > 350 pmol/L *Confirmation:* Urine aldosterone > 200 mmol/day post oral salt loading	1.6 %
Ito et al., 2011 (19)	Japan	292 consecutive patients with untreated HT presenting to a health screening center	*Screening:* ARR > 70 pmol/mU *Confirmation:* ARR > 70 pmol/mU post-CCT	3.8 %
Westerdahl et al., 2011 (20)	Sweden	200 consecutive patients with newly diagnosed (untreated) HT at 6 GP practices	*Screening:* ARR > 65 pmol/mU *Confirmation:* FST (? cut off)	5.5 %
Fogari et al., 2007 (15)	Italy	3000 consecutive patients with HT from participating GPs	*Screening:* ARR > 85 pmol/mU *Confirmation:* PAC > 210 pmol/L post SST	5.9 %
Williams et al., 2006 (21)	US	347 volunteers with HT recruited from the advertisement	*Screening:* ARR > 85 pmol/mU and PAC > 220 pmol/L *Confirmation:* Urine aldosterone > 17 mcg/day post oral salt loading	3.2 %
Westerdahl et al., 2006 (22)	Sweden	200 patients with HT from 2 primary care areas	*Screening:* ARR > 60 pmol/mU *Confirmation:* PAC > 160 pmol/L post FST	8.5 %
Schwartz et al., 2005 (23)	US	118 patients with HT from the community previously recruited for another study	*Screening:* N/A *Confirmation:* Urine aldosterone > 12 mcg/day and PRA < 1 ng/mL/h post oral salt loading	13 %
Mosso et al., 2003 (25)	Chile	609 patients HT from two primary care centers	*Screening:* ARR > 84 pmol/mU *Confirmation:* PAC > 140 pmol/mU post-FST	6.1 %
Loh et al., 2003 (24)	Singapore	350 patients with HT from two primary care clinics	*Screening:* ARR > 70 pmol/mU and PAC > 420 pmol/L *Confirmation:* PAC > 280 pmol/L post SST	4 %
Gordon et al., 1993 (26)	Australia	52 participants in an antihypertensive drug trial	*Screening:* ARR > 100 pmol/mU *Confirmation:* PAC > 170 pmol/L post FST	12 %

ARR aldosterone-to-renin ratio; CCT captopril challenge test; FST fludrocortisone suppression test; GP general practitioner; HT hypertension; PA primary aldosteronism; PAC plasma aldosterone concentration; PRA plasma renin activity; SST saline suppression test *All units of measurements have been converted into SI units using the following conversion: PAC 1 ng/dL = 27.7* pmol/L*; direct renin concentration (DRC) 1 ng/L = 1.6 mU/L; and plasma renin activity 1 ng/mL/h = DRC 8.2 mU/L*

clinical practice. In particular, PA is easily mistaken for essential hypertension given the mean age of diagnosis at 50 years [13, 14] and the common occurrence of normokalemia [45]. Secondly, patients with complications and multiple co-morbidities were less likely to undergo screening. This is likely due to the difficulty of interpreting aldosterone and renin test results in the presence of multiple medications and less perceived benefit in the setting of severe end-organ damage [46]. The need for "ideal" testing conditions to measure and interpret plasma aldosterone and renin concentrations adds another layer of complexity in screening for PA. Geographical inequality in PA screening was reported as an additional barrier to PA screening by a study from Thailand in which patients who lived further from a tertiary center were found to be less likely to undergo PA screening [47].

Primary care is where most patients with hypertension are seen, and so understanding the perception of primary care providers toward PA is crucial [48]. A qualitative interview-based study of GPs involved in a PA screening research program in Australia [49] identified several factors that influenced screening, including knowledge, cost and convenience, risk conceptualization, and improving



▶ **Fig. 1** Challenges for primary aldosteronism (PA) detection and potential strategies to address them.

clinical care. Many GPs found it challenging to cease common antihypertensive medications to obtain a more meaningful ARR [49]. Although the ARR can sometimes still be interpreted in the presence of interfering antihypertensive medications, GPs often found this difficult. Most GPs found it easy to screen for PA in patients with treatment-naïve hypertension but believed that it was costly and inconvenient to screen patients who were already taking antihypertensives [49]. GPs were also more likely to screen for PA in patients who they deemed were more likely to benefit from the diagnosis, such as those patients with resistant hypertension, although ironically testing is often more difficult in this group due to multiple interfering medications. Conversely, they were less likely to screen older patients with mild hypertension, and patients with features of metabolic syndrome or other cardiovascular risk factors considered to have essential hypertension [49]. Finally, GPs were more enthusiastic about screening younger patients as a PA diagnosis and targeted treatment in these patients would lead to less medication burden and lower cardiovascular complications in the long term, compared to a PA diagnosis in older patients who may be perceived as being less likely to derive substantial benefit [49]. This approach likely contributes to the under-diagnosis of PA, as many patients with PA in fact develop hypertension in their 50 s [14].

Another study investigating factors that influence GP screening for PA in Germany identified high laboratory costs for PA screening as a barrier [50]. This contrasted with the Australian GP study which reported that ARR analysis was relatively inexpensive [49]. German GPs, like the Australian ones, found the need for medication switching to be burdensome [50]. GPs were also used to dealing with an uncertain diagnosis and were willing to try spironolactone empirically without requiring a definite PA diagnosis [50]. Another factor that had been raised was the lack of awareness of the Endocrine Society PA testing guidelines. Only 50 % of GPs included in a survey in Italy and Germany were aware of this guideline which could explain the low rate of screening even in patients who were at high risk of having PA [37]. A study that reviewed 12 PA guidelines published between 2006-2016 found that the quality of the guidelines, with a few exceptions, was mostly poor and none were easily implementable [51].

Several other studies, although not primarily designed to assess factors influencing screening, also shed some light on this topic. Patient visits with internal medicine physicians including endocrinologists, nephrologists, and cardiologists were associated with higher rates of screening than visits with primary care physicians [8, 9]. This could reflect inadequate awareness or resources to screen for PA in primary care. Another approach to understanding this under-appreciation of PA is to look at what is missing. While the Endocrine Society has published guidelines on PA screening, this topic is almost absent from general hypertension guidelines [1, 52]. For instance, the 2017 American College of Cardiology/American Heart Association and the 2018 European Society of Cardiology guidelines only very briefly mentioned PA in the context of managing patients with resistant hypertension [53, 54]. These guidelines are more frequently utilized by clinicians who manage patients with hypertension than the Endocrine Society guidelines, and the inadequate emphasis on assessment for secondary causes of hypertension likely contributes to the low awareness of PA.

Strategies to improve the detection of primary aldosteronism

As discussed above, low awareness of PA is an important contributing factor to the sub-optimal detection rate. In a previous study

from our group, 30-minute education sessions on PA were provided to thirty GP practices in Victoria, Australia, and the GPs were then asked to screen patients with treatment-naïve hypertension for PA [14]. This resulted in 14 % of hypertensive patients being diagnosed with PA [14]. This was in stark contrast to the < 0.1 % rate of PA among hypertensive patients managed by Victorian GPs based on a survey conducted prior to the commencement of the study [39]. Thus, GP education is highly effective in improving the detection of PA, although the impact of education was variable among the GPs [14]. Hence, additional interventions would be needed to achieve a uniform increase in PA screening. Another important finding from this study was that measuring the ARR at the time of hypertension diagnosis, prior to the commencement of antihypertensive medication, was effective in diagnosing PA [14]. This reduced the complexity of needing to switch antihypertensive medications. In a follow-up survey, GPs overwhelmingly reported a preference for testing prior to starting medications [49]. Such an approach has been found to be cost-effective in a health economic study in a Chinese healthcare setting [55].

Another strategy that has been shown to improve PA detection is the provision of specialized clinics. The establishment of a dedicated Endocrine Hypertension Clinic in Victoria, Australia led to increased referrals being made from primary care rather than tertiary care. When the clinic was first established, only 20 % of the referrals came from primary care. By the third year, the proportion of primary care referrals had increased to 50 % [56]. This was reflected in the complexity of patients being referred; in the first year, 60 % of patients referred had difficult-to-manage hypertension, 40 % had end-organ damage, and only 3 % had early-stage hypertension [56]. In contrast, after three years, only half of the patients referred had difficult-to-manage hypertension and 34 % had end-organ damage. The proportion referred with early-stage hypertension increased to 19 % [56]. Similarly, higher rates for PA detection and treatment were found in Calgary, Canada compared with other parts of the Alberta province following the establishment of a specialized endocrine hypertension unit there [40]. The proportion of hypertensive patients that were screened for PA in the Calgary zone was 1.71 % compared with 0.19-0.28 % in other zones. Thus, the provision of a dedicated clinic with a streamlined process may improve PA detection.

Several other strategies had been proposed to improve the detection of PA, although these strategies had not been systematically studied; these could form the basis of future research. One suggestion is to increase the involvement of GPs and other clinicians involved in caring for people with hypertension and ask them to measure renin in each one of their patients with hypertension, regardless of the medications that they are taking [57]. Most of the commonly used antihypertensive medications, with the notable exception of beta blockers, tend to increase renin. If despite those interfering medications the renin is still suppressed, further investigations would be warranted [57]. With this simplified approach, some patients with PA may be missed due to a falsely normal renin, but many more will be detected than at present. Further studies on appropriate diagnostic thresholds for patients who take interfering medications may help to refine the approach.

Improving the detection of PA will require a coordinated multidisciplinary approach. Hypertension is a common condition encountered by a wide range of health professionals, from primary care nurses to GPs, endocrinologists, cardiologists, nephrologists, internal medicine specialists, and stroke physicians. Conversely, current hypertension guidelines have not placed an emphasis on PA, despite it being the most common and a potentially curable endocrine cause of secondary hypertension. Out of the 142 publications cited in the 2020 International Society of Hypertension guidelines for hypertension management, there was only one citation related to PA. This was the same number of citations as for coffee and licorice [57, 58]. For change to occur, stakeholders and policymakers need to be engaged to facilitate the implementation of research outcomes while the next generation of health professionals needs to be educated about the importance of PA to dispel the myth that it is a rare disease [57]. Consumer advocacy also plays a very important role in increasing awareness of PA. One example of this is the Primary Aldosteronism Foundation (www.primaryaldosteronism.org), a non-profit patient initiative that is serving the PA community worldwide and advocating for improved diagnosis and treatment of PA [59].

Conclusion

Hypertension is one of the leading risk factors for cardiovascular disease, contributing to 7 % of global disability-adjusted life years [60, 61]. While most patients have "essential" hypertension, a significant proportion has PA [31]. Currently, PA is substantially underdiagnosed and only 1-2 % of all the expected cases are identified. Strategies such as educational sessions for GPs and the provision of dedicated endocrine hypertension services are effective in improving detection. However, much more work is needed to bring PA to the forefront of hypertension management. Standardization of the diagnostic process, an increased emphasis on hypertension guidelines, and education of current and future clinicians are all needed to improve the detection of PA. Ultimately, there is a need to convince all stakeholders that PA is not a rare disease and that it is a condition very much worth diagnosing.

Conflict of Interest

The authors declare that they have no conflict of interest.

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