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Diagnostic procedures for primary aldosteronism

Diagnostische Methoden für den primären Hyperaldosteronismus

Stefan Pilz[1,*], Andreas Tomaschitz[1,*] and Winfried März[2–4]

[1] Department of Internal Medicine, Division of Endocrinology and Nuclear Medicine, Medical University of Graz, Graz, Austria
[2] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria
[3] Department of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, University of Heidelberg, Heidelberg, Germany
[4] Synlab Center of Laboratory Diagnostics, Heidelberg, Germany

Abstract

Primary aldosteronism (PA) affects 5% to 10% of all patients with arterial hypertension and is mainly caused by either aldosterone producing adenoma or by idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia. Patients with PA demonstrate a significantly increased risk of cardiovascular and renal disease when compared to patients with essential hypertension. However, PA can effectively be treated underlining the importance of screening for and diagnosing of PA. Measurement of the aldosterone to renin ratio (ARR) should be performed as a screening test. Patients with an elevated ARR should undergo confirmatory testing for PA, which generally aims to evaluate whether elevated aldosterone levels are suppressible by salt and volume loading or ACE inhibitor therapy. In patients with PA, subtype classification is important to identify patients who are eligible for surgical adrenalectomy (unilateral disease) and to differentiate them from patients with bilateral disease who should be treated with mineralocorticoid receptor antagonists. Adrenal imaging using computed tomography is the first step in subtype classification. Adrenal venous sampling is the preferred method to differentiate between unilateral and bilateral disease, but the posture test can also be useful in selected patients. The present review provides a brief overview of the diagnostic procedures for PA. Nevertheless, we acknowledge that the diagnostic accuracy of screening and confirmation tests for PA is at present insufficiently validated and further studies are required.

Keywords: aldosterone; arterial hypertension; primary aldosteronism; renin.

*Correspondence: Stefan Pilz and Andreas Tomaschitz, Department of Internal Medicine, Division of Endocrinology and Nuclear Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria
Tel.: +43-650-9103667
Fax: +43-316-673216
E-Mail: stefan.pilz@chello.at; andreas.tomaschitz@gmx.at

Zusammenfassung

Ein primärer Hyperaldosteronismus (PHA) liegt bei 5% bis 10% aller Patienten mit arterieller Hypertonie vor und wird in den meisten Fällen entweder durch ein Aldosteron produzierendes Nebennierenadenom oder durch einen idiopathischen Hyperaldosteronismus aufgrund einer bilateralen adrenalen Hyperplasie verursacht. Patienten mit PHA haben, verglichen mit Patienten mit essentieller Hypertonie, ein signifikant erhöhtes Risiko für kardiovaskuläre und renale Erkrankungen, wobei der PHA sehr effektiv behandelt werden kann. Dies unterstreicht die Wichtigkeit des Screenings und der Diagnosestellung eines PHA. Die Messung der Aldosteron-Renin-Ratio (ARR) sollte als Screeningtest durchgeführt werden. Patienten mit einer erhöhten ARR sollten einem Bestätigungstest zugeführt werden, der darauf abzielt, zu evaluieren, ob die erhöhten Aldosteronwerte durch Salz- und Volumenbelastung bzw. durch eine ACE-Hemmertherapie supprimierbar sind. Eine Subtypenklassifizierung des PHA ist wichtig, um Patienten zu identifizieren, die mittels Adrenalektomie behandelt werden können (unilaterale Erkrankung) und sie von Patienten mit einer bilateralen Erkrankung zu unterscheiden, die mit Mineralokortikoid-Rezeptor-Antagonisten therapiert werden sollten. Eine radiologische Bildgebung mittels Computertomographie ist der erste Schritt in der Subtypenklassifizierung. Das Nebennierenvenensampling ist die beste Methodik, um zwischen unilateraler und bilateraler Erkrankung zu unterscheiden, wobei der Lagerungstest bei ausgewählten Patienten ebenfalls seine Berechtigung hat. In der vorliegenden Übersicht geben wir einen Überblick über die diagnostischen Methoden für den PHA, wobei wir anmerken, dass die diagnostische Genauigkeit der Screening- und Bestätigungsteste für den PHA derzeit nicht ausrei-

chend gut validiert ist und weitere Studien notwendig sind.

Schlüsselwörter: aldosteron; arterielle hypertonie; primärer hyperaldosteronismus; renin.

Introduction

Primary aldosteronism (PA) is characterized by aldosterone concentrations that are inappropriately high in relation to renin and that are not adequately suppressible by sodium loading [1–3]. Approximately 5% to 10% of all patients with arterial hypertension suffer from PA and the prevalence of PA is even higher among patients with resistant hypertension [1–3]. Even at the same blood pressure level, patients with PA are at increased risk of cardiovascular and renal disease when compared to patients with essential hypertension [4–7]. Milliez et al. reported that patients with PA had a 4.2 times higher risk of stroke, a 6.5 times higher risk of non-fatal myocardial infarction and a 12.1 times higher risk of atrial fibrillation than patients with essential hypertension matched for age, sex, and systolic and diastolic blood pressure [4]. However, after medical or surgical treatment of PA, the cardiovascular outcome of patients with PA is not significantly different from those with essential hypertension [7]. Therefore, detection and treatment of PA is of significant potential benefit for hypertensive patients [7, 8]. However, accurate screening for PA is often not performed among hypertensive patients, which seems to be partially attributed to the fact that PA represents a diagnostic challenge. We aim to provide a brief overview of the diagnostic procedures for PA in the present review.

Historical perspective and pathophysiology

In 1954, Jerome W. Conn studied a 34-year-old female patient who suffered from arterial hypertension, cramps, and intermittent paralysis, and revealed hypokalemia, hypernatremia and metabolic alkalosis by laboratory testing [9]. Conn observed elevated aldosterone levels and the patient was cured after surgical removal of an adrenal adenoma. This first case of PA well illustrates the pathophysiologic effects of aldosterone hypersecretion. Aldosterone, which is synthesized in the zona glomerulosa of the adrenal glands and exerts effects on gene expression through the mineralocorticoid receptor, increases potassium excretion and stimulates sodium and water retention through the epithelial sodium channel (ENaC) which causes volume expansion and arterial hypertension if aldosterone secretion is inappropriately high [10]. In addition, it has recently been discovered that aldosterone exerts a variety of genomic and non-genomic effects, which are relevant for vascular and metabolic diseases [10, 11]. Angiotensin II is believed to be the main stimulus for aldosterone secretion, which is therefore under tight control of the renin-angiotensin system. However, aldosterone synthase is also stimulated by potassium and ACTH and a number of modulating factors requiring further exploration in detail [10, 11]. In the current concept of PA, aldosterone secretion is relatively autonomous from the renin-angiotensin system, whereas ACTH stimulation seems to have an important impact [10, 11]. In PA, renin levels are usually suppressed due to sodium and volume overload which inhibit renin secretion. However, a challenging problem in the diagnosis of PA is to differentiate if relevant alterations of renin and/or aldosterone levels are due to dysregulation of the renin angiotensin aldosterone system itself, or are secondary due to disturbed homeostasis of sodium balance [12, 13]. In this context, the disease entity of low-renin essential hypertension is characterized by relatively normal plasma aldosterone levels despite suppressed renin activity [12, 13]. Low-renin essential hypertension is believed to be partially related to dysfunction of the ENaC with subsequently increased sodium and volume retention which may be sufficient to suppress plasma renin activity but insufficient to reduce aldosterone synthase activity [13]. Interestingly, it is speculated that low-renin essential hypertension and PA represent a continuum in which environmental (e.g., sodium intake) and genetic factors (aldosterone synthase) play an important role [12].

Subtypes of PA

Subtypes of PA include idiopathic hyperaldosteronism (IHA) which is generally caused by bilateral adrenal hyperplasia (65% of all cases with PA) and aldosterone producing adenoma (APA) (30%) of the adrenal gland [3]. Additional subtypes of PA encompass primary unilateral adrenal hyperplasia (3%), aldosterone-producing adrenocortical carcinoma (1%), aldosterone-producing ovarian tumor (<1%), or other ectopic aldosterone-producing adenoma or carcinoma (<0.1%). Familial forms of PA include familial hyperaldosteronism type 1 (FH-1) which is also referred to as glucocorticoid-remediable aldosteronism (GRA) (<1%), FH-2 (familial occurrence of aldosterone-producing adenoma and/or IHA) (unknown frequency), and FH-3 (unknown frequency) [3, 14].

Screening for PA

There is an ongoing debate if all patients with arterial hypertension or only selected patients with a high prevalence for PA should be screened for PA. The challenge is that patients with advanced stage of arterial hypertension have a higher probability of PA, but diagnosis of PA at early/mild stage of arterial hypertension would be important to prevent the excess cardiovascular risk associated with the disease. Importantly, hypokalemia, representing the classical biochemical hallmark of

PA is only observed in a minority of patients with PA (9%–37%) [1].

According to the Endocrine Society Practice Guidelines [1], it is currently recommended to screen for PA in groups with relatively high prevalence for inappropriate aldosterone secretion:

- patients with moderate/severe arterial hypertension (Joint National Committee stage 2 (160–179/100–109 mm Hg) and stage 3 (>180/110 mm Hg);
- drug resistant hypertension;
- hypertension and spontaneous or diuretic-induced hypokalemia;
- patients with an adrenal incidentaloma (incidentally discovered adrenal mass) plus arterial hypertension;
- patients with a family history of early-onset hypertension or cerebrovascular accident at a young age (below 40 years);
- all hypertensive first-degree relatives of patients with PA [1].

There is general consensus that measurement of the aldosterone to renin ratio (ARR) should be used as the screening test for PA [1–3]. An elevated ARR indicates that aldosterone secretion is inappropriately high with regard to the activity of the renin-angiotensin system, which is considered to be the main regulator of the aldosterone levels by exerting a stimulatory effect of angiotensin II on aldosterone secretion. Hiramatsu et al. introduced the measurement of the ARR as a screening tool for PA already in 1981 [15], and several studies have confirmed that ARR reveals better diagnostic accuracy for PA compared to the isolated determination of potassium, aldosterone, or renin [16–20].

Laboratory methods for analysis of renin and aldosterone are critical for accurate diagnosis of PA. However, partially inadequate standardization, poor inter-laboratory reproducibility, and limited comparability of different assays represent problems in screening for PA.

Comparing four immunoassays for aldosterone, it was shown that absolute aldosterone levels were dramatically different despite good overall correlation of these assays [21]. Mass spectrometry is the gold standard for aldosterone measurements and according to recent findings it is urgently needed to harmonize and standardize currently used aldosterone immunoassays by calibration against a mass spectrometric reference method [21]. Alternatively, rapid, reliable and simple liquid chromatography-tandem mass spectrometry methods could be introduced in daily clinical practice of aldosterone determinations [22].

Renin can be quantitated by measuring plasma renin activity (PRA) which is determined by measuring the rate of renin catalyzed angiotensin I production from endogenous angiotensinogen, or by measuring plasma renin concentration (PRC) with a monoclonal antibody against renin [1, 23]. Assays for PRC have the advantage of shorter incubation times compared to determinations of PRA, but measurements of the low-renin range are in general more precisely performed with assays for PRA [24]. Another problem with PRC assays is the cryoactivation of prorenin to renin which may falsely elevate PRC [24]. Given that different assays for PRC and PRA are currently used in clinical practice, and considering the relatively high intra- and inter-laboratory coefficients of variation for renin measurements, it will be an important goal for future research to further validate these different assays and to improve the intra- and inter-laboratory reproducibility [24, 25].

Another key problem with the ARR is that many factors, such as concurrent drug therapy, posture, time of blood sampling, or dietary salt intake, have been shown to alter aldosterone and/or renin levels. Concerning medical therapy, consensus exists that all drugs which interfere with aldosterone-mediated effects, such as spironolactone, eplerenone, canrenoate, amiloride and triamterene, should be withdrawn for at least 4 weeks before ARR measurement. However, several other antihypertensive drugs also have an impact on aldosterone and/or renin levels [1, 26–28]. In particular, beta-blockers elevate the ARR which is mainly mediated by their suppressive effect on renin secretion, and ACE inhibitors or angiotensin II type 1 receptor blockers reduce the ARR. It should also be noted that diuretics may decrease ARR by stimulating renin release due to hypovolemia and hyponatremia. In this context, several studies have confirmed that the use of certain drugs is associated with significantly altered ARR values, but this does not necessarily mean that they also significantly alter the diagnostic accuracy of the ARR [1, 26–29]. Towards this, a study among 118 patients with essential hypertension has shown that discontinuation of antihypertensive drugs did not significantly alter (improve) the diagnostic accuracy of the ARR [29]. Ongoing controversy whether certain drugs should be withdrawn before screening for PA warrants future studies to clarify this important research question, because withdrawal of antihypertensive medications may harm patients.

Severe hypokalemia which inhibits aldosterone secretion should be restored before measurement of the ARR. Apart from this, it is currently recommended that patients should have unrestricted dietary salt intake before screening for PA, although it should be noted that the suppressive effect of sodium on renin levels might falsely elevate the ARR, and the impact of dietary salt loading on the diagnostic accuracy of the ARR has not been sufficiently validated [1]. According to current guidelines, ARR should be determined in the morning and after seating for 5–15 min in order to standardize the influence of circadian rhythms and the stimulatory effect of posture on renin and aldosterone levels. Interestingly, Tanabe et al. have shown that even under standardized blood sampling conditions there is a significant intra-individual variation of the ARR, suggesting that repeated measurements of ARR should be performed when screening for PA [30]. These variations in the ARR may also reflect the impact of other regulators of aldosterone secretion, such

as ACTH, or factors influencing renin which is, e.g., stimulated by sympathetic activity and inhibited by vitamin D [11, 31].

At present, the most adopted cut-off value for a positive screening test for PA is an aldosterone to PRA ratio of 30 (aldosterone in ng/dL divided by PRA in ng/mL/h), corresponding to an aldosterone to PRC ratio of 5.7 (aldosterone in ng/dL divided by PRC in ng/L) [1]. Some groups also use a cut-off value for aldosterone levels (e.g., 15 ng/dL) in addition to a cut-off for the ARR, because this may avoid false positive results due to very low renin levels but may also increase the risk for overlooking patients with PA [1].

Confirmatory testing

Patients with a positive screening test should undergo a confirmation test to establish inappropriate autonomous hypersecretion of aldosterone. Recommended tests are the saline infusion test (SIT), oral salt loading test, fludrocortisone suppression test (FST), and the captopril test. Overall, these tests aim to reveal that aldosterone is non-suppressible by salt and volume loading which inhibits renin secretion, or by decreasing the conversion of angiotensin I to angiotensin II with the use of captopril [32–39]. In detail, the SIT is performed by infusing 2 L of 0.9% saline i.v. over 4 h starting at 08:00–09:30 h. After the infusion, plasma aldosterone levels are measured and PA is diagnosed in patients with an elevated aldosterone level. The used cut-off values for aldosterone after the SIT vary between 5 and 10 (13) ng/dL, depending on the laboratory assays [35]. During the oral sodium loading test, the patients should increase their dietary sodium intake to $>$200 mmol/day for 3 days. Patients are considered to have a positive test if 24-h urinary aldosterone is $>$12 μg and 24-h urinary sodium content is $>$200 mmol [1, 32]. The FST is by some authors considered as the gold standard test for diagnosing PA, but this test requires hospitalization for 3 to 4 days with intake of fludrocortisone tablets together with salt and potassium supplementation and is less practicable [32, 36]. During the captopril test, patients receive 25–50 mg captopril and blood is drawn at baseline and after 1 or 2 h [1]. In patients with PA, aldosterone levels are not suppressed by captopril and renin levels remain low. It should be noted that recent data suggest that the captopril test may be misleading in some cases [1, 37]. In general, current evidence from the literature does not clearly favor one confirmation test over the other and an urgent need for better evaluation of the diagnostic accuracy of these confirmatory tests exists. For clinical routine, the confirmatory test for PA should be selected by considering the clinical and laboratory expertise as well as the patient's current clinical situation, including comorbidity, stage of hypertension, current medical treatment, as well as compliance issue.

Subtype classification

Subtype classification of PA is important to guide adequate treatment in patients with PA. Current guidelines recommend adrenal computed tomography (CT) in order to exclude adrenocortical carcinoma and adenoma as the first step of subtype classification in cases of confirmed PA [1, 40, 41]. Magnetic resonance imaging has shown neither higher sensitivity nor specificity in detecting adrenal tumors. However, adrenal CT scan is characterized by several limitations and only approximately 60% of adrenal masses are discovered [42, 43]. Small APAs might be misinterpreted as IHA, or conversely adrenal microadenomas might be mistaken as areas of hyperplasia. A key problem is the high prevalence of endocrine inactive incidentalomas in older patients [44]. Non-functioning unilateral macroadenomas may be hardly distinguishable from APAs and unilateral adrenal hyperplasia might be easily missed by the radiologist. In summary, an adrenal CT scan has limited accuracy in distinguishing between unilateral and bilateral aldosterone-producing adrenal lesions and should only be interpreted in the context of further diagnostic investigations [42].

The next step in subtype classification is selective adrenal venous sampling (AVS), which involves blood sampling from the right and left adrenal vein in order to differentiate between unilateral hypersecretion of aldosterone which can be surgically treated by removal of the affected adrenal gland, and bilateral aldosterone hypersecretion which can be treated by mineralocorticoid receptor antagonists [1]. Patients who should not undergo AVS include those with GRA who can be treated with glucocorticoids, patients with adrenal carcinomas who should be referred to oncologic treatment, and patients younger than 40 years old with a solitary unilateral adrenal adenoma identified by CT scan because they are highly suggestive for PA due to APA and can thus be surgically treated without AVS. Expert opinion recommends that all other patients with confirmed PA considering surgical options in the management of hypertension should undergo AVS irrespective of previous CT findings [1, 45].

AVS is usually performed by using the percutaneous femoral vein approach and blood is drawn from both adrenal veins and from a peripheral vein (either from a peripheral line or from a sheath sample) or the vena cava inferior [1, 45–48].

Cortisol and aldosterone are measured in the samples. Several centers use cosyntropin infusion during AVS (50 μg cosyntropin/h starting 30 min before AVS), because this should minimize stress-induced fluctuations in aldosterone secretion, maximize aldosterone secretion

from APA, and maximize the cortisol secretion from both adrenal glands thereby facilitating the evaluation of a successful catheterization of the adrenal veins by measurements of cortisol gradients between the adrenal and peripheral veins [1, 45–47]. When cosyntropin is used, successful catheterization of the adrenal veins is confirmed when the plasma cortisol level of the adrenal vein is at least 5 times higher than the cortisol concentration in the peripheral vein. When cosyntropin is not used, this cortisol gradient should at least be 3 to 1 [45, 47]. To correct for dilutional inflow of adjacent veins, e.g., the inferior phrenic vein, into the adrenal veins, it is recommended to calculate the aldosterone to cortisol ratio (cortisol-corrected aldosterone levels) and use this ratio to evaluate if lateralization of adrenal aldosterone hypersecretion exists [1, 45–47]. A ratio of these cortisol-corrected aldosterone levels of more than 4 to 1 between the two adrenal veins indicates lateralization of aldosterone hypersecretion, whereas a ratio of less than 3 to 1 indicates bilateral adrenal hypersecretion and a ratio in between is considered a gray zone [45]. Centers not using cosyntropin infusion during AVS use lower cut-off values, such as a ratio of 2 to 1 to confirm lateralization [1, 45, 46]. Catheterization of the adrenal veins, in particular the right adrenal vein, is a difficult task which requires an experienced radiologist. Some centers collect several samples from each of the presumed right and left adrenal veins to increase the possibility of obtaining an adequate adrenal venous sample [48]. In addition, rapid cortisol assays which can be used to measure cortisol levels during the AVS may increase the success rate of AVS [49]. In experienced hands, the success rate of AVS can be up to 96% with a complication rate (e.g., symptomatic groin hematoma, adrenal hemorrhage, or dissection of adrenal veins) of 2.5% or less [45]. The sensitivity and specificity of the AVS for detection of unilateral adrenal aldosterone production have been reported to be 95% and 100%, respectively [45, 46].

Further tests that have been evaluated for use in subtype classification of PA which may be particularly relevant for patients with unsuccessful AVS include the posture test and adrenal scintigraphy [1]. The posture test is based on observations that APAs are relatively unaffected by angiotensin II levels, whereas IHA showed enhanced sensitivity to an increase of angiotensin II occurring with standing [1, 50–52]. This test is performed by measuring aldosterone levels in the morning with the patient in supine position and after 2–4 h of continued erect position [50–52]. A fall in aldosterone (or 18-hydroxycortisone) levels (positive posture test) is suggestive of APA and an increase of aldosterone indicates IHA. However, the diagnostic accuracy of the posture test has been controversially discussed due to inconsistent study results [1, 50–52]. Given that a positive posture test has a high positive predictive value (specificity) of up to 100%, some authors recommend to perform adrenalectomy in PA patients with a solitary adrenal nodule on CT and a positive posture test [1, 51, 52]. The role of the adrenal scintigraphy ([131I] norcholesterol [NP-59]) in differentiation between APA and IHA has recently been evaluated [53]. Only limited sensitivity for correct lateralization of PA was established, but it was suggested that adrenal scintigraphy, similar to postural testing, might be a possible alternative diagnostic method in the case of inconclusive AVS.

Familial forms of PA should also be considered in the subtype classification of PA. Genetic testing for FH-1 by means of Southern blot or PCR techniques is currently recommended in patients with early onset of PA (e.g., $<$20 years) or with a positive family history of PA or stroke at a young age [1, 54, 55]. FH-1 is an autosomal dominant genetic disorder that is caused by a chimeric *CYP11B* gene that contains sequences of the *CYP11B1* gene (encoding for aldosterone synthase) and sequences of the *CYP11B2* gene (encoding for 11β-hydroxylase). This chimeric enzyme produces aldosterone throughout the entire adrenal cortex and not only in the zona glomerulosa as normal, and its expression is under the tight control of ACTH. FH-1 can be successfully treated with glucocorticoids in order to suppress pituitary ACTH production and is therefore also known as GRA. It should be noted that genetic testing for GRA should be performed before AVS in order to avoid unnecessary AVS in patients with GRA. Tests for autosomal dominant FH-2, whose molecular basis is unresolved at present although recent data suggest linkage to chromosome 7p22, and for the recently described FH-3 are not part of the current clinical routine [1, 56].

Treatment of PA

Unilateral laparoscopic adrenalectomy is the preferred treatment for PA patients with unilateral adrenal aldosterone hypersecretion. After removal of the affected adrenal gland, patients with APA are cured from hypertension in approximately half of the cases with an improvement of hypertension in the remaining cases [1, 57, 58]. Surgical therapy is considered cost-effective because it is significantly less expensive than long-term medical treatment [59]. Of note, spironolactone therapy should be performed before surgery in order to avoid post-surgical hypoaldosteronism [60]. Towards this, we should note that fludrocortisone therapy should be initiated in the case of post-surgical hypoaldosteronism which is usually associated with hyperkalemia and arterial hypotension [60]. PA patients with IHA or those with unilateral adrenal aldosterone hypersecretion who do not accept surgery or are not in condition for surgery respond well to drug therapy with mineralocorticoid receptor antagonists [1, 7, 60, 61]. It should be underlined that regular measurements of potassium and blood pressure are important in the initial phase of mineralocorticoid receptor antagonist

therapy. As outlined above, patients with GRA should be treated with glucocorticoids.

Conclusions

Diagnosing PA followed by targeted treatment of the disease is important to reduce the excess cardiovascular risk associated with this disease which is found in 5% to 10% of hypertensive patients, but is frequently not diagnosed. We presented a brief overview of the diagnostic procedures for PA acknowledging that diagnostic accuracy of the presented screening and confirmatory tests for PA is still not sufficiently well documented [62]. Controversy exists on the diagnostic work-up for PA which is responsible for the immense diversity in the approach different centers perform diagnostic procedures for this disease. This points to the urgent need for further studies to evaluate the diagnostic accuracy of the screening and confirmation tests for PA. We therefore designed the Graz Endocrine Causes of Hypertension (GECOH) study to prospectively evaluate the accuracy of the ARR and the SIT and the influence of drug therapy on their test characteristics as well as to compare different laboratory methods for the measurement of renin and aldosterone [63]. We anticipate that results of the GECOH study and other studies will significantly improve the knowledge about the diagnostic procedures for PA so that screening and diagnosing PA will be based on improved evidence and will therefore be more widely introduced to reduce the numbers of unrecognized PA in hypertensive patients.

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