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Primary Aldosteronism: A Glimpse into the Most Common Endocrine Cause of Arterial Hypertension

Gian Paolo Rossi and Teresa M. Seccia

Abstract

Compelling evidences showed that primary aldosteronism (PA) is a quite common disease. In spite of this, hypertensive patients are seldom screened for PA and, therefore, many patients are mislabelled as (low-renin) essential hypertension thereby remaining exposed to the nefarious consequences of long-term hyperaldosteronism. In this chapter we reviewed the clinical aspects of PA and the evidences supporting the need of implementing strategies aimed at diagnosing early PA patients. After reporting the prevalence rates of PA in different cohorts of hypertensive patients, we examined the reasons why PA is rarely searched for. The cardiovascular and renal damage associated with PA were also discussed, with particular emphasis to endothelial dysfunction, vascular remodeling, left ventricular changes, fibrosis, diastolic dysfunction, atrial fibrillation and chronic kidney disease. Studies supporting the concept that PA-associated organ damage can be prevented and even regressed with a timely diagnosis were also reviewed. A flowchart illustrating the proposal of a simplified diagnostic algorithm for screening and subtyping of PA, which allows circumventing the complexity of a diagnostic workup centred on confirmatory tests, is also proposed. Finally, the principles of treatment for PA are discussed.

Keywords: endocrine hypertension, primary aldosteronism, subtyping, diagnosis, adrenal vein sampling, outcome

1. Epidemiology

Primary aldosteronism (PA) is regarded by most practicing physicians as a 'needle in the haystack' [1], notwithstanding compelling evidences supporting the opposite view that is quite common. At the dawn of this millennium, based on small single-centre retrospective studies, the prevalence rate of PA was estimated to range from 1.4–32% (median 8.8%), i.e. so widely that no firm conclusions could be drawn on how common PA was, likely because of differences in the selection of the patient's cohorts and heterogeneous diagnostic criteria used in the various studies [2].

In 2006, the PA Prevalence in Hypertensives (PAPY) study, a prospective survey of consecutive newly diagnosed hypertensive patients referred to specialized hypertension centres, exploited for the first time use of a predefined protocol and standardized diagnostic criteria to diagnose PA [3]. This seminal study provided

solid evidences that among referred hypertensive patients the prevalence of PA was high, i.e. 11.2% [3]. Moreover, by calling attention to the fact that the only subtype of PA that could be diagnosed with certainty is aldosterone-producing adenoma (APA), this study introduced the ‘four-corners criteria’ to diagnose PA due to APA, a concept thereafter adopted in the PASO criteria [4] and recently revised to take into consideration the availability, thanks to Gomez-Sanchez’s laboratory, of a monoclonal antibody for human aldosterone synthase (CYP11B2) that allowed the immunohistochemical demonstration of aldosterone biosynthesis in adrenocortical nodule(s) of excised adrenals [5, 6].

It should be acknowledged, though, that estimates of the prevalence of PA are meaningless figures without specification of the cohort of hypertensive patients that are being considered. For example, in a general population survey in Japan, Ito et al. reported a prevalence of PA of 6.8% in prehypertensive subjects and 3.3% and 3.2%, respectively, in stage I and II hypertensive patients [7]. In the Bussolengo study, which involved hypertensive patients seen in general practice in Verona province in Italy, 34% were found to have an elevated aldosterone-to-renin ratio (ARR) suggesting PA [8]. Although the actual rate of those with confirmed PA remained uncertain, because no further tests could be undertaken, those findings suggested a high prevalence of PA among such unselected hypertensive patients. In line with this suggestion, in a similar study involving general practitioners in Torino (Italy), 5.9% of the patients were found to have PA [9]. Altogether these results led to the proposal that the screening for PA should be wider [10] than a screening only in selected categories of patients recommended by current guidelines [11].

Undoubtedly, screening should be exploited in patients with drug-resistant hypertension, which represent the cohort at the highest cardiovascular risk, not only because of the uncontrolled blood pressure (BP) values, but also because of the common concurrence of hypertension-mediated organ damage (HMOD) [9, 11–14]. In a single-centre study carefully carried out in Greece by Douma et al. in drug-resistant hypertension patients, who were studied after wash-out from interfering drugs, 20.6% were found to have a high ARR [15]. The rate fell to about 11% when the authors used the BP-lowering response to spironolactone to confirm their diagnosis. They considered this rate to be not as high as they expected [15]. However, yet unpublished data from the AVIS-2 study, the largest registry of patients submitted to adrenal vein sampling (AVS) for the subtyping of PA worldwide, indicated

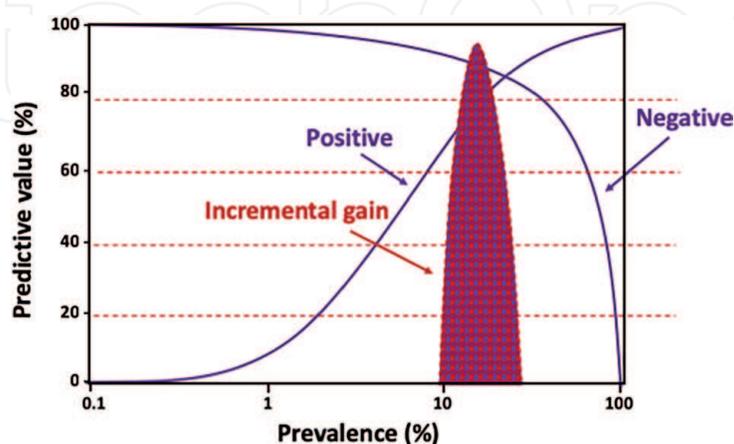


Figure 1.

Prevalence of a disease affects positive and negative predictive values. Furthermore, the diagnostic gain of a test is maximized when the prevalence of the disease is between 10 and 30%. Since primary aldosteronism (PA) was found to involve 11.2% in the hypertensive patients referred to the specialized centres for hypertension, and to be even more prevalent in the ‘resistant’ hypertensives, implementation of the screening strategies for PA furnishes an unambiguous gain in these categories, besides being of crucial relevance for identifying the patients who can benefit of the targeted treatment.

that between 20.1 and 49.5% of PA patients, depending on the criteria used to define this condition, have drug-resistant hypertension. Hence, resistant hypertension is a common presentation of PA. On the whole, these results showed that, at least among referred hypertensives who are carefully investigated, more than 11% have PA, with a rate that increases together with the stage of hypertension.

Hence, besides supporting the original contention of Conn [16], these findings showed that PA is by no means an exceptionally rare cause of human hypertension. Therefore, they have implications of paramount importance for the implementation of screening strategies in the hypertensive patients as the diagnostic gain of a diagnostic test is maximized when the prevalence of the disease that is sought for is between 10 and 30% (**Figure 1**).

2. Why PA is under-detected?

In spite of the fact that compelling evidences support the notion that PA is a common curable form of secondary hypertension, this condition remains markedly underdiagnosed for a number of reasons. The first is the misbelief that it is rare and therefore it is not worth of a search. The second entails the fact that hypokalaemia, which for decades has been considered the hallmark of PA, occurs only in less than half of the hypertensive patients, with APA and in less than 20% of those with bilateral adrenal hyperplasia (BAH, also known as idiopathic hyperaldosteronism, IHA) [3]. The third reason is a general phenomenon in medicine: the time lag occurring between publication of scientific data, their incorporation into practice guidelines and implementation of guidelines' recommendations in clinical practice. A survey of general practitioners in Italy and Germany documented that this is true also for PA: only 1 and 2%, respectively, in these countries were ever screened for PA by their general practitioners [17]. The fourth major reasons for the underscreening and consequent underdiagnosis of PA relate, in our view, to the fact that the diagnostic workup of patients for PA is perceived by practicing physicians as too complex to undertake and interpret. The recommended measure to prepare the hypertensive patients pharmacologically with a complete wash-out from drugs, which is totally unjustified, or better a switch to non-interfering drugs before undertaking the screening tests, is perceived as risky, even though evidence supporting the safety of a transient withdrawal of antihypertensive treatment exists [18, 19]. Uses of different assays to measure renin and aldosterone and of different units of measure are further factors undoubtedly confusing the interpretation of the screening test, which led us to develop an app that has been made freely available to address these difficulties [20] (<https://siia.it/attivita-ricerca/iniziativa/una-app-per-calcolare-l-arr/>).

As a result of the under diagnosis, far too many PA patients are misdiagnosed as (low-renin) essential hypertension and remain exposed to the nefarious consequences of long-term exposure to hyperaldosteronism [21, 22], which are described in the next section.

3. Cardiovascular and renal damage associated with PA

Patients with PA have higher cardiovascular morbidity and mortality than age-, sex- and BP-matched patients with essential hypertension [9, 13, 14, 23, 24]. This is because aldosterone excess, in the presence of a normal-to-high salt intake, has deleterious effects on the cardiovascular system that aggravate those of high BP, as convincingly demonstrated in both experimental and clinical studies [25–28].

In 1991, Karl Weber's and Richardo Rocha's laboratories provided unambiguous evidences that uni-nephrectomized salt-fed rats infused with aldosterone developed prominent inflammation and fibrosis in the heart and kidneys. Moreover, they showed that these changes could be prevented by pretreatment with mineralocorticoid receptor antagonists, as spironolactone, even at sub-antihypertensive doses, suggesting that aldosterone can cause fibrosis independently of its pressor effects [25, 29]. Moreover, in animal models, aldosterone infusion was shown to cause endothelial dysfunction via reactive oxygen species (ROS) generation; increased expression of NADPH oxidase subunits p22phox, gp91phox and p47phox; formation of peroxynitrite; oxidation of the NOS cofactor BH4 (5,6,7,8-tetrahydrobiopterin); and decreased G6PD (glucose-6-phosphate dehydrogenase) [30, 31].

In 1996, at a time when PA was still regarded as a 'benign' form of arterial hypertension, we reported that PA patients developed more left ventricular (LV) hypertrophy (LVH) than age-, sex- and BP-matched essential hypertensive patients, [32] and that this was particularly evident in those who showed more florid PA phenotypes due to an APA [13]. These findings were thereafter extended to show that they are more prone to develop fibrosis, atrial fibrillation [33], vascular remodeling [34], endothelial dysfunction [35, 36], increased carotid intima-media thickness and femoral pulse wave velocity, more frequently than those with essential hypertension [13, 14, 32, 37].

Moreover, the occurrence of LVH, LV fibrosis, impaired diastolic function, atrial dilatation and electric remodeling in PA (rev in [38]) explains why these patients were found to have a 12-fold higher risk of developing atrial fibrillation, the most common arrhythmia worldwide, than essential hypertensive patients in a French retrospective study [39]. Accordingly, adrenalectomy was found to lower the risk of atrial fibrillation in PA patients in the long-term longitudinal phase of the PAPY study [33]. Collectively these evidences support the concept that aldosterone favors atrial fibrillation [38] and that PA patients are more susceptible to heart failure with onset of atrial fibrillation [13, 40] because of a 'stiffer' LV causing LV diastolic dysfunction and fibrosis, which lead to a greater dependency of the LV on the atrial kick for its filling.

PA patients also develop more renal damage with development of proteinuria and/or chronic kidney disease. In 1988, Danforth et al. first reported moderate to severe renal parenchymal damage in renal biopsies of patients with PA [41], a finding confirmed two decades later by Nishimura et al. [42] and, in 2006, by the PAPY study, which reported higher albumin excretion rate in PA patients than in matched essential hypertensives [14].

The important notion to be considered in this context is that most of the hypertension-mediated organ damage associated with PA can be prevented and even regressed, at least partially, with a timely diagnosis. For example, in a long-term observational study, long-term regression of LVH and a decrease incidence of AF were documented [43]. Moreover, in the longitudinal phase of the PAPY study, we found that incident AF was significantly decreased by adrenalectomy, but not by long-term medical treatment [33]. In line with such findings Hundemer et al. [40] reported that PA patients with persistently suppressed renin despite treatment with mineralocorticoid receptor antagonists had a higher risk of AF than essential hypertensives, or patients on treatment with mineralocorticoid receptor antagonists and increased renin (suggesting optimal mineralocorticoid receptor blockade), or adrenalectomized PA patients.

A long-term follow-up study by Sechi et al. [44] showed that in PA renal damage could be reversed by target treatment, a finding thereafter supported by Hundemer et al. [45], who showed that glomerular filtration rate declined more in PA patients treated with mineralocorticoid receptor antagonists than in essential

hypertension patients and in PA cured with adrenalectomy. Rapid regression of microalbuminuria in PA suggests that urinary albumin excretion is, at least in part, due to functional rather than structural renal changes, i.e. glomerular hyperfiltration and decreased intrarenal vascular resistance. Elegant studies by Hall et al. in dogs exposed to hyperaldosteronism while renal perfusion pressure was maintained constant support this contention [46].

Thus, early screening and identification of PA patients who need surgery is needed to prevent/regress morbid events caused by hyperaldosteronism.

4. Screening of PA

The diagnosis of PA requires demonstration of an excessive aldosterone secretion autonomous of the renin-angiotensin system [11]. This implies concomitant measurement of plasma aldosterone and renin levels, Na⁺ and K⁺ in serum and 24-hour urine, followed by calculation of the aldosterone-to-renin ratio (ARR) [11]. Nowadays, the measurement of direct renin concentration has replaced plasma renin activity (PRA) in many laboratories because it is simpler, quicker and more accurate in the low range typically seen in PA [47]. However, the optimal cutoff value of the ARR is still a matter of debate and for optimal use they should be determined at each centre. Based on a prospective validation using a solid diagnosis of PA due to APA diagnosed as previously mentioned, we use 2.06 ng/dl/mUI/L (=20.6 ng/mUI) if renin is estimated by DRC or 26 ng/dl/ng/ml/h if renin was measured as PRA [47]. The aforementioned ARR-App can render the interpretation of results straightforward for practicing physicians and avoids the errors that might occur with unit conversion and calculations [20].

5. Confirmatory tests

Confirmatory tests are still used in most centres, even though there is clear-cut evidence that at the prevalence rate of PA seen in referral centres, i.e. between 11 and 30%, their negative predictive value largely exceeds their positive predictive value [48], and, therefore, these tests function as 'exclusion tests'. These tests stand on the unproven hypothesis that aldosterone secretion is unresponsive to maneuvers that perturbate renin. By such premise, they will identify only the subset of PA cases that are unresponsive to salt or volume suppression of aldosterone secretion, notably a minority of the cases of PA [6, 49].

Therefore, as discussed in depth elsewhere, this is a highly controversial issue [49]. Most studies supporting the use of these tests did not follow the STARD recommendations [50]: they attempted to validate the confirmatory tests not against a gold reference standard, as the diagnosis of APA, but against another confirmatory test, also based on the presumed autonomy of aldosterone secretion from the renin-angiotensin system [49]. Therefore, they were affected by a tautology bias. The only demonstration of CYP11B2-positive nodules at pathology, besides biochemical cure of PA after adrenalectomy, provides, in our view, a conclusive diagnosis of PA, which can be an APA or unilateral multinodular adrenocortical hyperplasia [5]. Given the availability of monoclonal antibodies for human CYP11B2, we recently amended the 'four corners' with the addition of immunohistochemical detection of CYP11B2 in the resected adrenal for the diagnosis of APA [3]. Likely considering the complexity and the intrinsic inaccuracy of the confirmatory tests, the last Endocrine Society guidelines for the first time foresaw the possibility of skipping these tests in patients with a florid PA phenotype and to proceed directly to subtyping (see later) [11].

Simplified Algorithm for The Work-up of PA

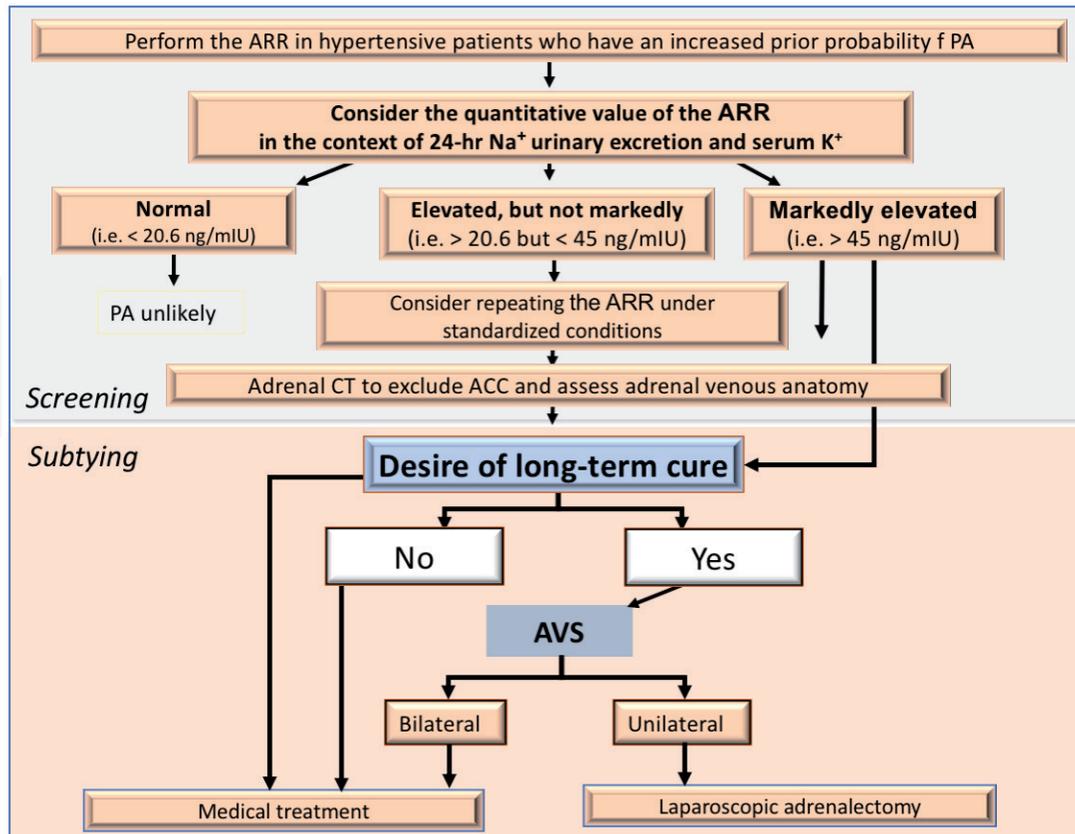


Figure 2.

The flow-chart describes a simplified diagnostic algorithm for the work-up of primary aldosteronism (PA). The work up is schematically divided into screening, which is based on measurement of plasma aldosterone and renin and levels and calculation of the aldosterone-to-renin ratio (ARR), and subtyping that requires adrenal vein sampling (AVS). In the screening, given the important information conveyed by the quantitative value of the ARR, this test should not be regarded as positive or negative. Instead its actual value should be used to stratify the patients for probability of PA. The ARR value must be assessed in the context of 24-hr Na^+ urinary excretion and serum K^+ . See text for explanation. Given the unreliable results of the so called “confirmatory tests”, the authors do not recommend their use. A clear-cut advantage of this algorithm is its simplicity with ensuing cutting costs and, moreover, its being feasible in most centres. AVS is key for subtyping of primary aldosteronism (PA), which is indicated only in patients wishing to accomplish long-term cure. Adrenal imaging by CT should be performed preliminarily to AVS for two main reasons: to exclude malignant neoplasms (adrenocortical carcinoma, ACC) and to assess the anatomy of adrenal veins which can guide interventionists in performing AVS.

In a recent large-size study comprising an exploratory and validation cohort, we investigated the accuracy of one such ‘confirmatory’ tests, the captopril challenge. This study provided unambiguous evidence that when a solid diagnosis of APA was used as reference index, the quantitative information conveyed by the ARR was accurate enough to avoid use of any confirmatory tests and to skip confirmatory tests [51]. In fact, neither the fall of plasma aldosterone concentration after captopril administration nor the fall of the ARR value furnished any diagnostic gain over baseline ARR values in these two very large cohorts of patients [51]. These results call for a simplification of the diagnostic algorithm as depicted in **Figure 2**. This strategy decreases the complexity, costs and time of the diagnostic workup for PA and therefore could extend the screening to most hypertensive patients, even in municipalities with low levels of access to specialized medical care.

6. Subtyping of PA

The most common forms of PA are unilateral causes of PA, mostly APA and rarely unilateral multinodular hyperplasia, and bilateral forms (BAH or IHA).

As unilateral PA is best treated with unilateral laparoscopic adrenalectomy, while bilateral forms require lifelong mineralocorticoid receptor antagonists, the distinction between APA and IHA is crucial for choosing the appropriate treatment [11, 52].

There are at least 10 key reasons why AVS should be used to reliably discriminate between unilateral and bilateral PA, as reviewed in depth elsewhere [53]. AVS, albeit minimally invasive and safe [54], is technically difficult and expensive and potentially affected by several factors [55, 56]. For these reasons it should be performed only in properly selected patients and in centres with a skilled multidisciplinary team that has extensive expertise [11]. As a preliminary test for adrenalectomy, it should be reserved for patients seeking long-term cure of PA with surgery, who are reasonable candidates for general anesthesia and adrenalectomy. Importantly, AVS should be performed after correction of hypokalaemia, if present, and adjustment of antihypertensive medications to allow correct interpretation of the AVS results [11]. Patients with genetically confirmed familial forms of PA [57] usually have bilateral forms of PA and therefore should not be submitted to this test unless they have a CT detectable node.

7. Treatment of PA

The Endocrine Society guidelines [11] state that a lateralized aldosterone secretion should be demonstrated before undertaking surgery in patients who are candidates for general anesthesia and wish to achieve long-term cure. Laparoscopic adrenalectomy is currently the best treatment that it can be performed during a short hospital stay at a very low operative risk [58].

Overall, surgery cured PA in 33–72% of patients and resulted in marked improvements in 40–50% of patients [54]. This wide variation of results is explained by the fact that at some centres adrenalectomy is performed on the basis of imaging alone that can be misleading in a substantial proportion of patients [54]. When performed after demonstration of lateralized aldosterone, excess adrenalectomy cured or determined a marked improvement of hypertension in ~82% of the patients, while practically all were biochemically cured from the hyperaldosteronism [54]. Even when antihypertensive treatment cannot be withdrawn after adrenalectomy, the number and/or the doses of antihypertensive drugs could be markedly decreased, and/or resistant hypertension was resolved at long term [54]. Adrenalectomy can also lead to a considerable improvement in several indexes of quality of life.

The outcome for blood pressure was found to be predicted by the duration of hypertension and vascular remodeling, both of which are associated with delayed diagnosis (28). Overall available evidence supports the concept that the sooner the diagnosis is made and adrenalectomy performed, the better the outcome [54]. Failure to achieve cure of PA can be the result of concurrent essential hypertension or an inaccurate diagnosis (AVS not performed or results incorrectly interpreted). In fact, both the PASO study [4] and the larger AVIS-2 study (manuscript submitted) showed a huge variability in AVS success even at major referral centres. Due to the high prevalence of both PA and primary (essential) hypertension, up to one third of patients with PA would be expected to have concurrent primary hypertension. Adrenalectomy can cure only PA, but not hypertension, in these patients.

For patients who are not candidates for surgery or do not show lateralized aldosterone excess, a treatment based on mineralocorticoid receptor antagonists, such as spironolactone, canrenone, potassium canrenoate and eplerenone (which is more selective but also more expensive, weaker and shorter acting than the other antagonists and is not generally available), is a reasonable alternative to adrenalectomy.

Spironolactone was found to regress LVH even at doses (37 mg daily) that did not completely normalize BP in both PA and low-renin hypertension, supporting a role of aldosterone in LVH development [59]. The occurrence of gynaecomastia and impotence, the more annoying side effects of the mineralocorticoid receptor antagonists, is dose-dependent, which suggests the use of reduced doses in combination, if necessary, with other agents, such as long-acting calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Amiloride and triamterene have been also proposed in addition to the first-line treatment with mineralocorticoid receptor antagonists if BP control is not optimal [60], but these drugs are not available as single agent in some countries, and, moreover, the combined therapy needs monitoring of serum potassium and creatinine. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can be particularly useful, as they effectively control the counter-regulatory stimulation of the renin-angiotensin system triggered by the diuretic action of the mineralocorticoid receptor antagonists. Aldosterone synthase inhibitors are also being developed and tested in phase III trials as an effective strategy to control hyperaldosteronism [61, 62].

8. Future developments

Mutations in the selectivity filter of potassium channels of the KCNJ5 type and other genes involved in the regulation of cytosolic calcium in adrenocortical cells [57, 63] play an important role in upregulating aldosterone secretion. Few germline mutations associated with bilateral adrenal hyperplasia and severe PA have been identified, thus allowing identification of further forms of familial hyperaldosteronism (6). These discoveries have triggered enormous investigative efforts, whose results, which are difficult to anticipate at this time, might lead to change our understanding and our diagnostic and therapeutic approach to PA. For the time being, following a few simple rules and a streamlined approach (**Figure 2**), physicians can successfully and cost-effectively identify and treat many patients with the so-called 'essential' hypertension whose high blood pressure is instead caused by hyperaldosteronism. In these patients the clue to PA is a low plasma renin, which responds little nothing to stimulatory maneuvers. Identification of PA is particularly beneficial when hypertension is severe and/or resistant to treatment, because specific treatment can bring blood pressure under control despite withdrawal or a prominent reduction in the number and dosage of antihypertensive medications.

Acknowledgements

This publication is based upon the work from the EU COST Action ADMIRE BM1301 in Aldosterone and Mineralocorticoid Receptor Physiology and Pathophysiology www.admirecosteu.com. The authors' work herein reviewed was supported by research grants from FORICA (the Foundation for advanced Research in Hypertension and Cardiovascular diseases), the Società Italiana dell'Ipertensione Arteriosa and grants from the Ministry of University and Scientific Research (MIUR) and The University of Padova.

Conflict of interest

Both authors have read and approved the manuscript. There is no conflict of interest and financial disclosure.

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