Renin and Aldosterone Measurements in the Management of Arterial Hypertension

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Abstract
Renin-angiotensin-aldosterone system (RAAS) is recognized as the main regulatory system of hemodynamics in man, and its derangements have a key role in the development and maintenance of arterial hypertension. Classification of the hypertensive states according to different patterns of renin and aldosterone levels (“RAAS profiling”) allows the diagnosis of specific forms of secondary hypertension and may identify distinct hemodynamic subsets in essential hypertension. In this review, we summarize the application of RAAS profiling for the diagnostic assessment of hypertensive patients and discuss how the pathophysiological framework provided by RAAS profiling may guide therapeutic decision-making, especially in the context of uncontrolled hypertension not responding to multi-therapy.

Introduction
Since the discovery of renin in 1898 by Tigerstedt [1], our comprehension of the renin-angiotensin-aldosterone system (RAAS) has grown progressively [2, 3] and this hormonal cascade is now recognized as the main regulatory system of hemodynamics in man. According to Poseuille’s law, the main determinants of pressure in a hydraulic system are the overall resistance of the conduit and the fluid flow passing through it. Considering the vascular system, these factors consist of vascular resistance, due to systemic vascular tone, and cardiac output, which is directly related to preload and, hence, to blood volume, respectively. Several important mechanisms and physiological systems have been implicated in the control of blood pressure (BP) levels both in the short- and long-term [2]. In the steady state, however, the key role of the RAAS has been demonstrated, as it can affect both peripheral vascular resistance and kidney sodium handling and, therefore, circulating volume. In fact, on the one hand angiotensin-II is itself a vasopressor agent and is able to stimulate the secretion of another potent endogenous vasopressor, arginine-vasopressin. On the other hand, angiotensin-II directly enhances sodium reabsorption in the proximal tubule and stimulates the production of aldosterone, that is responsible for sodium reabsorption in the distal tubule [4]. Besides this classical view of the RAAS, several experimental studies on animal models have established the involvement of a local brain RAAS in the regulation of BP through central modulation of sympathetic efferents, baroreceptor reflex mechanisms, and renal tubular reabsorption [3, 5].

As previously stated, the main determinants of BP levels are vascular tone (the “resistance”, or “R-factor”) and circulating volume (the “volume”, or “V-factor”). Owing to the RAAS, these 2 factors are reciprocally regulated. Physiologically, in fact, hypovolemia triggers renin secretion, resulting in angiotensin-II-mediated vasoconstriction and angiotensin-II- and aldosterone-mediated sodium reabsorption, whereas increased circulating volume downregulates renin release and angiotensin-II generation, preventing further sodium reabsorption and especially decreasing peripheral vascular resistance. Circulating volume can primarily increase irrespective of activation of the renin-angiotensin-II axis (e.g., due to excessive sodium intake or primary aldosteronism), and this leads to renin suppression. In contrast, vascular tone in the steady state is mainly related to angiotensin-II-dependent vasoconstriction and, therefore, to renin activity. For these reasons, renin levels somehow...
circuiting volume (or “V-factor”) is better and independently described by body sodium content. In a normal circulatory system, the interaction between “R-factor” and “V-factor” allows the maintenance of BP in the normal range [6,7], and their fluctuations can be considered as an adaptive change under different hemodynamic conditions. In hypertensive states, the presence of either elevated renin levels or primary body sodium excess is antiphysiological and can be interpreted as the mechanism responsible for BP elevation [7,8], providing the basis for a pathophysiologic classification of arterial hypertension. From a practical point of view, evaluation of renin levels is more feasible in routine clinical practice than measurement of body sodium content. Moreover, primary sodium overload is expected to match low renin levels. This has prompted the traditional classification of arterial hypertension in high-renin, low-renin and normal-renin hypertension [9,10]. “High-renin” hypertension (HRH) has been interpreted as a disproportionate and sustained increase of peripheral resistance, whereas “low-renin” hypertension (LRH) may represent a condition of primary sodium-volume overload. In “normal-renin” hypertensive states, renin and circulating volume inappropriately maintain themselves in the normal range, without interdependent counter-regulation. It has been suggested that HRH and LRH, not only represent different pathophysiologic conditions but are also clinically distinct. Early studies showed a higher rate of cardiovascular events in HRH than in LRH, that was previously believed to be a “benign” condition [9,11]; later reports observed an association between HRH and an increased rate of coronary events and heart failure [12–14]. However, LRH was later shown to display a distinct pattern of cardiovascular events with a similar risk profile to HRH. In a study by Morimoto et al., “sodium sensitive” hypertensives showed a greater number of cardiovascular events in comparison to “non-sodium sensitive” (i.e., HRH) patients, and a large proportion of these events comprised stroke [15] that was not correlated to HRH in previous studies. To investigate RAAS activity, evaluation of renin and aldosterone levels can then give information in the initial evaluation of the hypertensive patient, as a marker of the main pathophysiologic alterations responsible for BP elevation. In this review, we will analyze how this classification can be useful in the clinical management of arterial hypertension.

### RAAS Profiling as a Tool for Diagnostic Classification of Secondary Hypertension

It has been shown that combined evaluation of renin and aldosterone levels (“RAAS-profiling”) allows the detection of specific patterns, which can suggest the presence of specific forms of secondary hypertension [16,17]. Cost-effectiveness of this approach has been demonstrated, especially in presence of resistant hypertension [18,19]. We herein summarize the main forms of secondary hypertension, which can be suspected with a given pattern of the RAAS profile.

#### High-renin hypertensive states

True HRH has been observed in a minority of the hypertensive population [10], although about 70% of patients fall into the group with “non-suppressed” renin values [10]. The main secondary causes of hypertension, which present with elevated renin levels are renovascular hypertension [20], pheochromocytoma [21,22], and hypertension related to oral contraceptive assumption [23] (Table 1). A very rare condition is renin-secreting juxtaglomerular cells tumor, or reninoma [24]. All these forms of hypertension are conditions of secondary aldosteronism, in which the increase in aldosterone is driven by the increase in renin levels. Among them, RAAS profiling – especially the determination of renin levels – has been applied for reninoma and renovascular hypertension because of remarkably high levels of renin often noticed in these disorders. Because of particular hyperresponsiveness of renin secretion in renovascular hypertension, a captopril test has been proposed for screening, considering renin response to a single dose of captopril [25]. Later evidence demonstrated the suboptimal accuracy of this test [20,26,27], perhaps due to a relevant number of patients with renovascular hypertension showing low-to-normal renin levels and a blunted response of plasma renin activity to captopril administration [26].

<table>
<thead>
<tr>
<th>Renin levels</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Elevated</td>
<td>Pheochromocytoma, Reninoma</td>
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<tr>
<td>Normal</td>
<td>Primary aldosteronism</td>
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<tr>
<td>Low</td>
<td>Secondary forms of hypertension</td>
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#### Table 1 Classification of hypertensive conditions by renin and aldosterone levels.

<table>
<thead>
<tr>
<th>Renin/Aldosterone states</th>
<th>Conditions</th>
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<tr>
<td>Low-renin/low-aldosterone</td>
<td>Gordon’s syndrome</td>
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<tr>
<td>Low-renin/normal-aldosterone</td>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>High-renin/low-aldosterone</td>
<td>Cushing’s syndrome (especially related to ectopic ACTH production)</td>
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* Depending on sodium intake and ongoing therapy, Gordon’s syndrome may also present with reduced or increased aldosterone levels

† Primary Aldosteronism can be considered even in case of low renin levels and high-normal aldosterone levels, the latter being inappropriately high in relation to renin suppression

# Only if renin is measured as plasma renin activity

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; COXIBs: COX-2 inhibitors; UFH: unfractionated heparin; UAMES: Apparent Mineralocorticoid Excess Syndrome; DOC: Deoxycorticosterone; 11β-Hydroxysteroid-dehydrogenase type 2; 11β-OHase: 11β-Hydroxylase; 17α-OHase: 17α-Hydroxylase; MR: Mineralocorticoid Receptor; ACE: Angiotensin-Converting Enzyme inhibitors; ARBs: Angiotensin-II Receptor Blockers; DRI: Direct Renin Inhibitors. Modified and adapted from [16]
Beyond “true” high-renin secondary forms of hypertension, it should not be forgotten that coexistence of high blood pressure and high renin levels may also often occur in the uncontrolled hypertensive treated with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARBs). These drugs, in fact, remove the negative feedback loop exerted by angiotensin-II on renin secretion and plasma renin activity by blocking production of angiotensin-II or its binding to angiotensin-II receptors type 1 (AT1-Rs). A correct interpretation of high renin levels in a hypertensive patients should then always prompt an evaluation of the ongoing medications.

Low-renin hypertensive states
Low-renin hypertension encompasses about 30% of hypertensive patients [10] and a number of secondary causes of hypertension falls into this group. In fact, all monogenic forms of hereditary hypertension so far discovered are related to renal electrolyte handling and determine an excessive sodium reabsorption, leading to suppression of renin levels [28]. Moreover, primary aldosteronism, the prototypical example of low-renin hypertension, has been acknowledged as the most frequent form of secondary hypertension [29].

Differential diagnosis of low renin forms of hypertension is clinically relevant, because different forms are treated with different therapies. A practical classification of low-renin hypertensive states is based on aldosterone levels [16] (Table 1). A close examination of clinical and pathophysiological features of these disorders is beyond the purpose of this review, and has been reported elsewhere [16]. Coexistence of low levels of both renin and aldosterone can be due to acquired or congenital disorders. Acquired causes encompass drugs, which suppress renin and therefore aldosterone secretion (β-blockers, central anti-adrenergic drugs such as clonidine and α-methyl-DOPA, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, unfractionated heparin) [30–32], conditions of significant reduction in nephron mass (chronic glomerulonephritis, diabetic nephropathy, unilateral nephrectomy or, simply, age) [16], or activation of mineralocorticoid receptors (MRs) by steroids different from aldosterone. This latter is the case of the “Apparent Mineralocorticoid Excess Syndrome” (AMES), in which an excessive licorice intake can suppress the physiologic activity of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2). Such inactivation prevents the conversion of cortisol and of others adrenal steroids with salt-retaining activity [38]. Finally, a deficit of 11β-hydroxylase or 17α-hydroxylase blocks cortisol production and elicits ACTH excess that drives the overproduction of DOC [39, 40]. Besides low-renin essential hypertension, normal levels of aldosterone in the presence of low renin are found in Gordon’s syndrome, a genetically determined disorder of sodium and potassium transport in the distal renal tubule [41, 42]. This syndrome is characterized by an abnormally high reabsorption of both sodium and potassium, leading to hyperkalemia and hypervolemia, and by a remarkable responsiveness to thiazide diuretics. Usually, sodium and potassium balances have reciprocal effects on aldosterone secretion, so that aldosterone is maintained in the normal range. Variations in dietary sodium intake and diuretic therapy can alter aldosterone production, and patients with Gordon’s syndrome may show even reduced or increased aldosterone levels [43]. Primary aldosteronism (PA) may even present, in milder forms, with low renin coupled with inappropriately high-normal levels of aldosterone, although very high levels of aldosterone that are renin-independent constitute the characteristic feature of this disorder. Diagnosis of PA entails 3 steps, namely a screening test, a confirmation/exclusion test to definitively distinguish it from low-renin essential hypertension, and subtype classification to recognize familial forms and separate unilateral from bilateral disease [44]. An early and accurate diagnosis of PA is important both for its prevalence and its clinical impact. In fact, PA accounts for 4.3% of hypertensives in the general population and up to 9.5% in referral centers [45]; moreover, PA patients show a higher risk of cardiovascular events in comparison to essential hypertension, and this excess risk may be completely reverted with a targeted therapy [46, 47]. Subtype classification of PA is key in determining the appropriate therapy. In fact, whereas a particular familial form, glucocorticoid-remediable aldosteronism, requires a treatment with low-dose glucocorticoids, bilateral forms (bilateral adrenal hyperplasia) are best treated medically with MRBs and unilateral forms (mainly aldosterone-producing adenoma) may be surgically cured by unilateral adrenalectomy [44].

Renin Levels as a Predictor of Response to Different Antihypertensive Drug Regimens

Variability of response to different anti-hypertensive drug classes
Heterogeneity of BP response to different antihypertensive agents is well-known among clinicians [48]. It was first recognized when earlier studies with diuretics and β-blockers reported a differential response to these drugs among hypertensive people [49–52]. Such variability of response was later con-
firmed also with other antihypertensive drug classes, such as ACEi and calcium channel blockers (CCBs) [53–59]. A milestone study by Materson and colleagues [55], in particular, compared the response to 6 different antihypertensive drugs and to placebo in a wide population of white and black men. This randomized trial observed a strong variability in response to several drugs across different ethnic groups and ages. This then allowed the formulation of an "age-race rule" that was proposed as a guide to initial choice of antihypertensive treatment [48]. Materson’s observations were somehow confirmed by subsequent prospective cross-over studies performed by Brown and colleagues [56,57]. The study population considered was young (aged less than 55 years) with a net prevalence of Caucasian people. In these trials, they observed larger BP decrease with ACEi and β-blockers and a consistence of individual response to ACEi and β-blockers and to CCBs and thiazide diuretics, but not in other pairs of drugs. Combining these results with those of previous studies [55,60] and, in particular, considering the findings of the ALLHAT study [58], Brown developed an algorithm, termed the “AB/CD-rule” from the capital letters of the main antihypertensive drug classes considered [61], that quickly summarized our knowledge about defined correlations between demographic characteristics and BP response to initial different drugs. According to the “AB/CD-rule”, the initial antihypertensive drug should be chosen between an ACEi, an ARB or a β-blocker (one from the “A-B” pair) in younger (i.e., <55 years old) Caucasian people and between a CCB or a thiazide diuretic (one from the “C-D” pair) in black or older (>55 years old) Caucasian patients.

Pathophysiological basis of BP response variability to different antihypertensive drugs – the Laragh’s hypothesis

The pathophysiological bases of BP response variability had been first investigated by Bühler, Laragh and colleagues, who observed a strong correlation between renin levels (determined as plasma renin activity) and the pattern of response to different antihypertensive drugs. In fact, people with medium or high renin activity showed a striking response to propranolol, a β-blocker, whereas people with low renin activity did not show a clinically significant BP reduction with this drug [49]. Rather, low-renin hypertension was observed to respond better to diuretics [62].

On this basis, Laragh postulated that all hypertensive disorders are due to a variable contribution of renin-dependent vasoconstriction and sodium-related circulating volume expansion. RAAS profiling was then proposed to define which – if any – of these 2 factors is predominant in sustaining BP elevation [63].

According to this “vasoconstriction-volume model”, all the antihypertensive drugs should somehow counteract one of the hypertension determining factors, either excessive vascular resistance (the “R-factor”) or expanded circulating volume (the “V-factor”). Antihypertensive agents may be therefore classified as “anti-R” or “anti-V” drugs [64] (Table 2).

Over the years, refining their observations, Laragh and colleagues developed a renin-based method to guide the choice of antihypertensive therapy [64] (Fig. 1). When renin activity falls into medium- to high-levels (PRA≥0.65 ng/ml/h) then an “anti-R” drug is indicated; with suppressed renin levels (PRA<0.65 ng/ml/h), instead, therapy should begin with an “anti-V” drug. If necessary, dose has to be increased to a maximal level. When BP is not controlled on monotherapy, then renin profiling can again be useful to investigate the current pathophysiological response to the initial therapy in the individual patient. In this case, suppressed renin levels indicate the need to add an “anti-V” drug. This is aimed at boosting the natriuretic effect in patients firstly already treated with an “anti-V” drug, and at balancing a residual action of the “V-factor” in patients previously treated with an “anti-R” drug. On the contrary, an unsuppressed PRA again indicates the need to add an “anti-R” drug. This allows to strengthen the anti-renin effect in patients firstly treated with an “anti-R” drug, and to counteract a concurrent action of the “R-factor” in people previously treated with an “anti-V” drug. To this end, considering that anti-RAAS agents manage in reducing about 90% of RAAS activity and that PRA assays measure renin enzymatic activity, it is important to underline the effect of different “anti-R” drugs on PRA levels. In fact, during therapy with agents that suppress renin secretion or inhibit its enzymatic activity (namely, centrally-acting antidiuretics, β-blocker and direct renin inhibitors), the cutoff to distinguish unsuppressed and suppressed PRA levels remains 0.65 ng/ml/h. With agents which inhibit angiotensin-II production or effects (ACEi and ARBs), the cutoff is ten-fold, 6.5 ng/ml/h, because the reactive increase in PRA levels along with the blockade of the downstream elements of the RAAS, that reduces the effective activity of the system to about 10% of the observed values [65].

Clinical confirmation and current controversies of Laragh’s hypothesis

Whilst Laragh developed his theory, many other authors investigated the pathophysiological bases of BP response variability to antihypertensive agents. Several observational studies confirmed the predictive value of renin levels to the response to β-blockers, thiazide diuretics, and mineralocorticoid receptor-blockers (for a review of these studies, see [66]). Other reports,
however, failed to observe an association between pre-treatment renin levels and response to β-blockers and/or diuretics [67–70].

Later, a number of studies investigated the association between pre-treatment renin profiling and response to anti-hypertensive drug classes other than β-blockers and diuretics. In a randomized trial, Weir et al. observed a lack of correlation between BP reduction and pre-treatment renin levels in a cohort of predominantly low-renin African-American hypertensives treated with trandolapril [71]. Another trial, however, reported a superior efficacy of β-blockers and ACEi in a population of young white patients in which PRA levels were associated to BP response to ACEi [56]. More recently, 2 small observational studies have also reported an association between pre-treatment renin levels and response to ARBs, considering not only office BP but also ambulatory BP monitoring [72, 73].

In 1998, Preston et al. published a post-hoc analysis on the data of the large study previously conducted by Materson, aiming at comparing renin profiling to the “age-race rule”. In this study, the BP response to a therapy appropriate to renin levels resulted not superior to the one obtained by an antihypertensive therapy fitting to age and ethnic group. The authors then concluded that the “age-race rule”, simpler and cheaper than renin profiling, was preferable as a guide to clinical decision-making [48]. Although a correlation through renin activity and age and ethnic group has been recognized for long time [9, 74], this correlation is not strict enough to allow an accurate prediction of renin levels on the basis of demographic data alone [10]. Moreover, the “age-race” rule is no more able to predict the response to a new antihypertensive agent when an antihypertensive therapy is already ongoing [64]. In fact, in subsequent observational studies, a head-to-head comparison of the “age-race rule” and renin profiling overturned the conclusions by Preston and colleagues. Schwartz et al. observed that renin profiling alone was superior to the “age-race rule” alone in predicting BP response to a therapy with candesartan or hydrochlorothiazide [75]. In an inter-
testing study, Turner et al. retrieved renin levels as the only parameter, beside pre-treatment BP, consistently able to predict systolic and diastolic response to both atenolol and hydrochlorothiazide, whatever the age and the ethnic group. Moreover, this study observed for the first time an association between in-treatment renin levels and response to add-on therapy [76]. Renin levels were also the only parameter significantly predictive of response to each of the 4 drugs used (bisoprolol, losartan, hydrochlorothiazide, and amlodipine) in a recent randomized cross-over trial that investigated laboratory predictors of BP reduction [77]. On the contrary, another recent trial conducted in elderly (> 70 years old) hypertensive patients failed to recognize an association between renin levels and BP response to valsartan and/or hydrochlorothiazide [78], whereas a recent observational study retrieved a significant association between renin levels and diastolic BP response and a trend towards an association between renin levels and systolic PB response [79]. On the whole, the studies so far presented reached conflicting conclusions about the predictive value of renin profiling: reasons for such an inconsistency have not been fully understood. A possible explanation can be suggested due to lack of appropriate control, in many of these studies, for concomitant medications such as non-steroidal anti-inflammatory drugs (NSAIDs), which heavily interfere with the RAAS affecting the response to anti-hypertensive therapy. Another explanation could reside in a differential activity of tissue-specific RAAS and systemic RAAS in the single patient: while, in fact, plasma renin activity may not accurately account for the level of activation of tissue-specific RAAS, it has been shown in animal models that selective activation of central nervous system-RAAS can produce an increase in systemic BP [5]. This latter point apparently challenges the theoretical basis of Laragh's method, even if it is based mainly on data derived from animal models. It should be noted that Laragh's pathophysiological classification of hypertensive phenotypes represents mainly a clinical classification. Its purpose is to suggest a rational approach to guide therapy in a field that is mainly empirical, although is potentially oversimplified. For example, the original Laragh's classification of antihypertensive drugs included reserpine as an “anti-R drug” and α1-adrenergic receptor blockers and direct vasodilators as “anti-V drugs” whereas available evidence in the literature do not support such a characterization.

It should be highlighted that to date only a small unblinded randomized trial has been performed to specifically investigate the validity of Laragh's hypothesis [80]. In this study, a group of patients whose therapy was adjusted strictly according to Laragh's method (renin-test guided therapy, RTGT) was compared to a group committed to clinical hypertension specialists care (CSHC). After follow-up, RTGT group, in comparison to CHSC group, showed a significant reduction in systolic BP, a trend towards a reduction of diastolic BP and a higher BP control rate, with no difference in the number of antihypertensive medications (which were the same as baseline) [80].

These data are not fully conclusive: a definite validation of “Laragh's method” should require a large, randomized clinical trial encompassing both naïve hypertensives and already-treated, uncontrolled patients. For this reason, one of the main concerns raised relates to the economic cost of renin levels determination [48]. To this end, some authors have reported an estimate of costs related to the application of renin-profiling in the initial examination of hypertensive patients [19,81], and observed that renin levels determination is quite cheap and warrants savings from an economic point of view. A more extensive cost-effectiveness study has been recently performed [82], suggesting that a renin-guided strategy may be cost-effective, at least for treated but uncontrolled patients, and could be even advantageous in all hypertensive patients if renin testing costs should decrease.

Although heterogeneity in BP response to different drugs has been thoroughly investigated and is a matter of fact, lack of a conclusive validation of Laragh's method has prevented its acknowledgement by many current national and international guidelines for the management of arterial hypertension [83,84]. The British Hypertension Society (BHS) – National Institute for Clinical Excellence (NICE) guidelines, however, early recognized the work by Brown and colleagues, so that since 2004, BHS-NICE guidelines recommend, for the uncomplicated hypertensive patients and in absence of compelling indications and contraindications, a choice of the initial antihypertensive therapy based on the “AB/CD rule” [85]. This one, in the light of the broadening evidence [86–88], has been later reduced to the “ACD rule” after the removal of β-blockers as first-line choice drugs [89]. BHS-NICE guidelines at the moment do not recommend renin profiling to guide the choice of therapy, relying only on demographic parameters. Nonetheless, they openly refer to Laragh's “vasostriction-volume model” as the main conceptual framework necessarily subtended to the individual variability in BP response to different drugs, and they assume the “age-race model” as an estimate of renin profiling [85]. Recently, even the recent report of the Eighth Joint National Committee (JNC-VIII) moved towards the acknowledgement of differential response to diverse antihypertensive agents and the personalization of therapy, accepting the evidence coming from subgroup analyses of the ALLHAT study [90] and the ASCOT-BPLA study [59]. Therefore, now the JNC-VIII guidelines recommend specifically a CCB or a thiazide diuretic for initial antihypertensive therapy among black people. In conclusion, current evidence reports some observations which are consistent with the pathophysiological basis of Laragh's method [56,57,77,91] and even suggests that RAAS profiling may be useful for management of essential hypertension [75,76,79], especially in complex situations with uncontrolled hypertension not responding to multitherapy [80]. At present, Laragh's method offers a “conceptual framework” that, supplemented with the global clinical picture, may guide clinical reasoning and decision-making in the single patient.

Conclusions

More than a century of experimental and clinical studies have recognized the central role of the renin-angiotensin-aldosterone system in regulation of hemodynamics and to classify different patterns of RAAS-profile. Along with clinical features and the epidemiologic context, RAAS profiling may orient towards diagnosis of specific forms of secondary hypertension characterized by a selective responsiveness to targeted therapies [16]. In particular, RAAS profiling allows the identification of primary aldosteronism, the most prevalent form of secondary hypertension, whose early diagnosis and targeted treatment is key to effectively reduce the cardiovascular excess risk for which this adrenal disorder is responsible [46,47]. Moreover, some data regarding essential hypertension suggests that RAAS profiling has the opportunity to clarify the main pathophysiological alter-
The authors declare no conflict of interest.

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Review


