

Renin and Aldosterone Measurements in the Management of Arterial Hypertension

Authors

A. Viola¹, S. Monticone¹, J. Burrello¹, F. Buffolo¹, M. Lucchiarì², F. Rabbia¹, T. A. Williams¹, F. Veglio¹, G. Mengozzi², P. Mulatero¹

Affiliations

¹ Division of Internal Medicine and Hypertension, Department of Medical Sciences, University of Torino, Torino, Italy
² Clinical Chemistry Laboratory, University of Torino, Torino, Italy

Key words

- arterial hypertension
- rennin
- aldosterone
- Laragh's hypothesis
- therapy

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 Poiseuille'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 may represent vascular tone ("R-factor") whereas

received 23.07.2014
accepted 12.03.2015

Bibliography

DOI <http://dx.doi.org/10.1055/s-0035-1548868>
Published online:
May 8, 2015
Horm Metab Res 2015;
47: 418–426
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0018-5043

Correspondence

A. Viola

Division of Internal Medicine
and Hypertension
Department of Medical
Sciences
University of Torino
Via Genova 3
10126 Torino
Italy
Tel.: +39/011/6336 959
Fax: +39/011/6336 931
andreaviola.83@gmail.com

circulating 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 pathophysiological 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

Table 1 Classification of hypertensive conditions by renin and aldosterone levels.

Low-Renin Hypertensive Conditions	
Low-renin/low-aldosterone states	
Acquired:	Low-renin essential hypertension
	Drugs (β -blockers; central antiadrenergic agents; NSAIDs; COXIBs; UFH)
	Reduced nephron mass (GNs; diabetic nephropathy; unilateral nephrectomy; ageing)
	Acquired AMES (licorice excess)
	Cushing’s syndrome (especially related to ectopic ACTH production)
	DOC-secreting adrenal tumors
Genetic:	Liddle’s syndrome
	Congenital AMES (mutations of 11 β -HSD-2)
	Congenital adrenal hyperplasia (11 β -OHase deficiency; 17 α -OHase deficiency)
	Glucocorticoid resistance syndrome
	MR-activating mutation
Low-renin/normal-aldosterone states	
	Low-renin essential hypertension
	Gordon’s syndrome *
Low-renin/high-aldosterone states	
	Low-renin essential hypertension
	Primary aldosteronism [§]
High-Renin Hypertensive Conditions	
	High-renin essential hypertension
	Reno-vascular hypertension
	Pheochromocytoma
	Reninoma
	Drugs (ACEi; ARBs; DRI; diuretics-all subclasses; oral contraceptives [#])

* 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; 11 β -Hydroxysteroid-dehydrogenase type 2; 11 β -OHase: 11 β -Hydroxylase; 17 α -OHase: 17 α -Hydroxylase; MR: Mineralocorticoid Receptor; ACEi: Angiotensin-Converting Enzyme inhibitors; ARBs: Angiotensin-II Receptor Blockers; DRI: Direct Renin Inhibitors. Modified and adapted from [16]

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].

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, ageing) [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 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2). Such inactivation prevents the conversion of circulating cortisol to cortisone, and cortisol can then act as a mineralocorticoid hormone [33]. This same result may occur with a primary cortisol excess in Cushing’s syndrome (especially with ectopic ACTH production, for the higher levels of cortisol produced) [34]. An adrenal tumor secreting deoxycorticosterone (DOC), an aldosterone precursor with mineralocorticoid properties, is an alternative but is a much rarer occurrence of MR activation by steroids different from aldosterone.

Among genetic disorders with low levels of both renin and aldosterone, those with BP elevation mediated by extrinsic activation of MRs can be distinguished from those whose hypertension is due to alterations downstream from the MR. These latter include constitutive activation of MRs [35] and Liddle’s syndrome, that is due to an increased activity of the epithelial sodium channel (ENaC), the main renal effector of MRs [36]. Both of these disorders do not respond to MR-antagonists, but respond well to amiloride, that directly blocks ENaC. Genetic disorders leading to the increased activation of MRs, include congenital AMES, the syndrome of glucocorticoid resistance, and the rarer forms of congenital adrenal hyperplasia (CAH)

associated with a functional deficit of 11 β -hydroxylase and 17 α -hydroxylase. In all these diseases, MR activation is due to an excess of a hormone with mineralocorticoid properties that is different from aldosterone, but whose binding to MRs can be prevented by MR-antagonists. In congenital AMES, an inactivating mutation in the gene for 11 β HSD2 causes an intracellular cortisol excess that results in its inappropriate binding to the MR [37]. In the syndrome of glucocorticoid resistance, the glucocorticoid receptor does not respond to cortisol and does not mediate pituitary feedback regulation of ACTH: this results in an excessive stimulation of the adrenals and an increased production of cortisol and of others adrenal steroids with salt-retaining activity [38]. Finally, a deficit of 11 β -hydroxylase or 17 α -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-

Table 2 Classification of antihypertensive drugs according to Laragh's hypothesis.

"Anti-V" Drugs	"Anti-R" Drugs
Natriuretic drugs – reduce sodium-related circulating volume	Anti-renin/Angiotensin-II drugs – reduce renin/angiotensin-II related vasoconstriction
Mineralocorticoid receptor blockers	Drugs suppressing renin activity
Thiazide and thiazide-like diuretics	Centrally acting α_2 -adrenergic receptor agonists
Loop diuretics	β -Adrenergic receptor blockers
Calcium-channel blockers	Direct renin inhibitors
	Drugs preventing angiotensin-II production or effects
	Angiotensin-converting enzyme inhibitors
	Angiotensin-II receptor blockers

"Anti-V" Drugs, "Anti-R" Drugs: see text. Modified and adapted from [64]

firmly 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 anti-hypertensive 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 consistency 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 ($PRA \geq 0.65$ 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 antiadrenergic drugs, 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 block its 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,

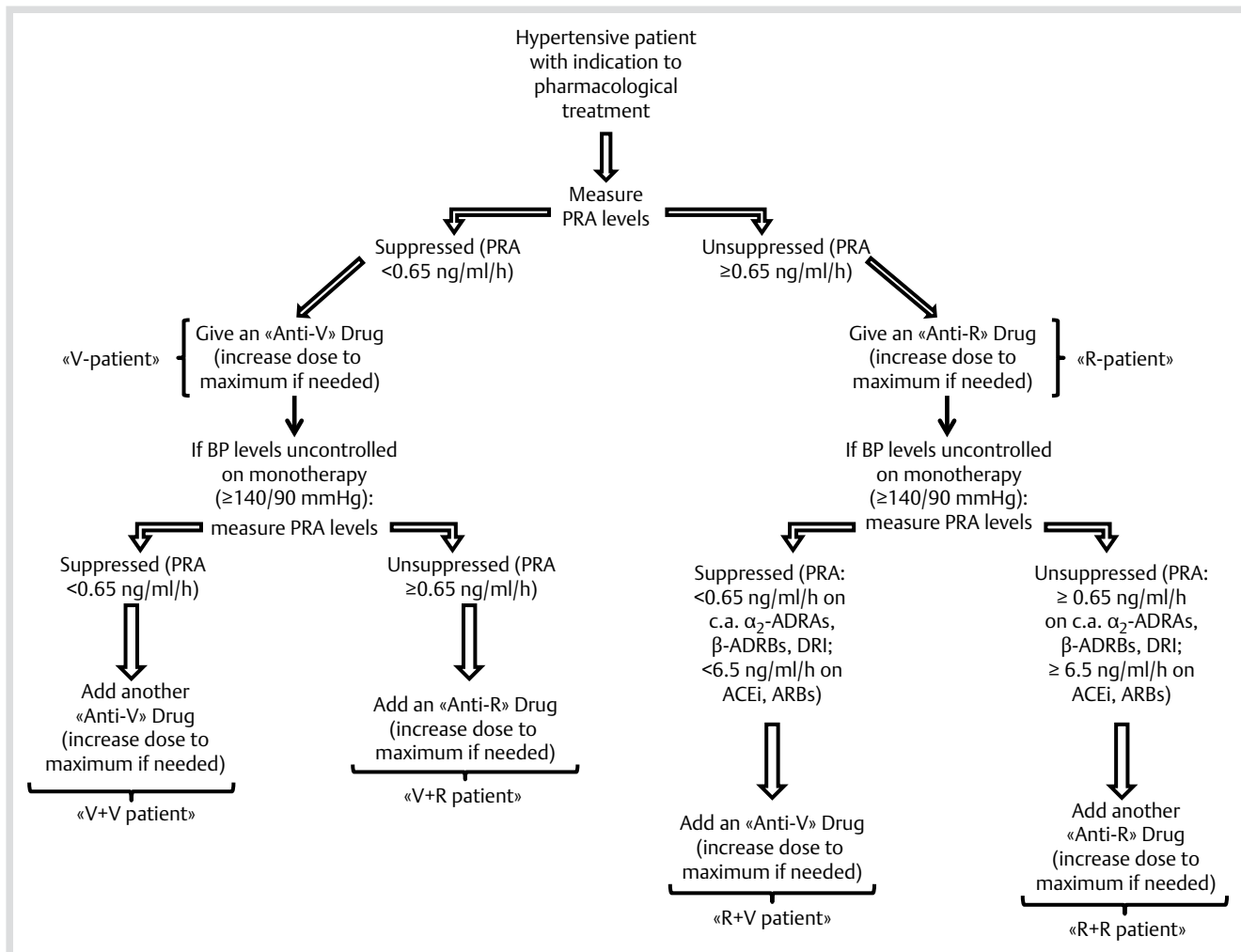


Fig. 1 Algorithm of Laragh's method for choice of antihypertensive treatment. R-drug, V-drug: see text; "V-patient": patient whose leading pathophysiological mechanism of hypertension is circulating volume expansion; "R-patient": patient whose leading pathophysiological mechanism of hypertension is angiotensin-II mediated vasoconstriction; "V+V patient": patient whose leading pathophysiological mechanism of hypertension is an extreme degree of circulating volume expansion; "V+R patient": patient whose hypertension is due mainly to circulating volume expansion but to some extent also to angiotensin-II mediated vasoconstriction; "R+V patient": patient whose hypertension is due mainly to angiotensin-II mediated vasoconstriction but to some extent also to circulating volume expansion; "R+R patient": patient whose leading pathophysiological mechanism of hypertension is an extreme degree of angiotensin-II mediated vasoconstriction. c. a. α_2 -ADRA: Centrally-acting α_2 -adrenergic receptor agonists; β -ADRBs: β -Adrenergic receptors blockers (β -blockers); DRI: Direct renin inhibitors; ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-II receptor blockers. Modified and adapted from [64].

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-

esting 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 α 1-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 (CHSC). 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 "vasoconstriction-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-

ations in the single patient and to guide clinical decision-making [75], especially in complex situations with uncontrolled hypertension not responding to multitherapy [80]. Although Laragh's method requires more extensive validation, it already represents a valuable "conceptual framework" for the hypertension specialist, establishing a connection between pathophysiology and clinics.

Conflict of Interest

The authors declare no conflict of interest.

References

- Basso N, Terragno NA. History About the Discovery of the Renin-Angiotensin System. *Hypertension* 2001; 38: 1246–1249
- Castrop H, Höcherl K, Kurtz A, Schweda F, Todorov V, Wagner C. Physiology of kidney renin. *Physiol Rev* 2010; 90: 607–673
- Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; 86: 747–803
- Weir MR, Dzau VJ. The Renin-Angiotensin-Aldosterone System: A Specific Target for Hypertension Management. *Am J Hypertens* 1999; 12: 205S–213S
- Takahashi H. Upregulation of the Renin-Angiotensin-Aldosterone-Ouabain System in the Brain Is the Core Mechanism in the Genesis of All Types of Hypertension. *Int J Hypertens* 2012, 242786
- Gavras H, Brunner HB, Vaughan ED, Laragh JH. Angiotensin-sodium interaction in blood pressure maintenance of renal hypertensive and normotensive rats. *Science* 1973; 180: 1369–1371
- Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Am J Med* 1973; 55: 261–274
- Luetscher JA, Boyers DG, Cuthbertson JG, McMahon DF. A model of the human circulation. Regulation by autonomic nervous system and renin-angiotensin system, and influence of blood volume on cardiac output and blood pressure. *Circ Res* 1973; 32: 84–98
- Brunner HR, Sealey JE, Laragh JH. Renin subgroups in essential hypertension. Further analysis of their pathophysiological and epidemiological characteristics. *Circ Res* 1973; 32: 99–105
- Alderman MH, Cohen HW, Sealey JE, Laragh JH. Plasma renin activity levels in hypertensive persons: their wide range and lack of suppression in diabetic and in most elderly patients. *Am J Hypertens* 2004; 17: 1–7
- Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, Bühler FR. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 1972; 286: 441–449
- Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med* 1991; 324: 1098–1104
- Gonzalez MC, Cohen HW, Sealey JE, Laragh JH, Alderman MH. Enduring direct association of baseline plasma renin activity with all-cause and cardiovascular mortality in hypertensive patients. *Am J Hypertens* 2011; 24: 1181–1186
- Tomaschitz A, Pilz S, Ritz E, Morganti A, Grammer T, Amrein K, Boehm BO, März W. Associations of plasma renin with 10-year cardiovascular mortality, sudden cardiac death, and death due to heart failure. *Eur Heart J* 2011; 32: 2642–2649
- Morimoto A, Uzu T, Fujii T, Nishimura M, Kuroda S, Nakamura S, Inenaga T, Kimura G. Sodium sensitivity and cardiovascular events in patients with essential hypertension. *Lancet* 1997; 350: 1734–1737
- Mulatero P, Verhovez A, Morello F, Veglio F. Diagnosis and treatment of low-renin hypertension. *Clin Endocrinol (Oxf)* 2007; 67: 324–334
- Verhovez A, Mulatero P, Bertello C, Saglio E, Viola A, Tosello F, Rabbia F, Veglio F. Is Renin-Based Treatment a Reasonable Strategy to Treat Essential Hypertension? *High Blood Press Cardiovasc Prev* 2008; 15: 1–5
- Spence JD. Stepped care for hypertension is dead, but what will replace it? *CMAJ* 1989; 140: 1133–1136
- Spence JD. Government guidelines for treatment of hypertension. *Am J Hypertens* 1995; 8: 541
- Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. *Circulation* 2005; 112: 1362–1374
- Song AL, Zeng ZP, Tong AL, Lu L, Chen S, Li M, Fu CL, Wang YH, Sun ML. Differences of blood plasma renin activity, angiotensin II and aldosterone levels in essential or secondary hypertension. (Article in Chinese) *Zhonghua Nei Ke Za Zhi* 2012; 51: 294–298
- Bernini M, Bacca A, Casto G, Carli V, Cupisti A, Carrara D, Farnesi I, Barsotti G, Naccarato AG, Bernini G. A case of pheochromocytoma presenting as secondary hyperaldosteronism, hyperparathyroidism, diabetes and proteinuric renal disease. *Nephrol Dial Transplant* 2011; 26: 1104–1107
- Laragh JH. Oral contraceptives – induced hypertension – nine years later. *Am J Obstet Gynecol* 1976; 126: 141–147
- McVicar M, Carman C, Chandra M, Abbi RJ, Teichberg S, Kahn E. Hypertension secondary to renin-secreting juxtaglomerular cell tumor: case report and review of 38 cases. *Pediatr Nephrol* 1993; 7: 404–412
- Muller FB, Sealey JE, Case DB, Atlas SA, Pickering TG, Pecker MS, Preibisz JJ, Laragh JH. The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986; 80: 633–644
- Rossi GP, Pavan E, Chiesura-Corona M, Bader M, Paganini G, Cesari M, De Toni R, Feltrin GP, Ganten D, Pessina AC. Renovascular hypertension with low-to-normal plasma renin: clinical and angiographic features. *Clin Sci (Lond)* 1997; 93: 435–443
- Lenz T, Kia T, Rupprecht G, Schulte KL, Geiger H. Captopril test: time over? *J Hum Hypertens* 1999; 13: 431–435
- Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001; 104: 545–556
- Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res* 2004; 27: 193–202
- Mulatero P, Rabbia F, Milan A, Paglieri C, Morello F, Chiandussi L, Veglio F. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension* 2002; 40: 897–902
- Gordon RD, Laragh JH, Funder JW. Low renin hypertensive states: perspectives, unsolved problems, future research. *Trends Endocrinol Metab* 2005; 16: 108–113
- Sealey JE, Gerten JN, Ledingham JG, Laragh JH. Inhibition of renin by heparin. *J Clin Endocrinol Metab* 1967; 27: 699–705
- Quinkler M, Stewart PM. Hypertension and the cortisol-cortisone shuttle. *J Clin Endocrinol Metab* 2003; 88: 2384–2392
- Cicala MV, Mantero F. Hypertension in Cushing's syndrome: from pathogenesis to treatment. *Neuroendocrinology* 2010; 92: 44–49
- Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, Meinke G, Tsai FT, Sigler PB, Lifton RP. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* 2000; 289: 119–123
- Warnock DG. Liddle syndrome: an autosomal dominant form of human hypertension. *Kidney Int* 1998; 53: 18–24
- Wilson RC, Nimkarn S, New MI. Apparent mineralocorticoid excess. *Trends Endocrinol Metab* 2001; 12: 104–111
- Stratakis CA, Karl M, Schulte HM, Chrousos GP. Glucocorticosteroid resistance in humans. Elucidation of the molecular mechanisms and implications for pathophysiology. *Ann N Y Acad Sci* 1994; 746: 362–376
- Zachmann M, Tassinari D, Prader A. Clinical and biochemical variability of congenital adrenal hyperplasia due to 11 beta-hydroxylase deficiency. A study of 25 patients. *J Clin Endocrinol Metab* 1983; 56: 222–229
- Takeda Y, Yoneda T, Demura M, Furukawa K, Koshida H, Miyamori I, Mabuchi H. Genetic analysis of the cytochrome P-450c17alpha (CYP17) and aldosterone synthase (CYP11B2) in Japanese patients with 17alpha-hydroxylase deficiency. *Clin Endocrinol (Oxf)* 2001; 54: 751–758
- Hadchouel J, Delaloy C, Fauré S, Achard JM, Jeunemaitre X. Familial hyperkalemic hypertension. *J Am Soc Nephrol* 2006; 17: 208–217
- Boyden LM, Choi M, Choate KA, Nelson-Williams CJ, Farhi A, Toka HR, Tikhonova IR, Bjornson R, Mane SM, Colussi G, Lebel M, Gordon RD, Semmekrot BA, Poujol A, Välimäki MJ, De Ferrari ME, Sanjad SA, Gutkin M, Karet FE, Tucci JR, Stockigt JR, Keppler-Noreuil KM, Porter CC, Anand SK, Whiteford ML, Davis ID, Dewar SB, Bettinelli A, Fadrowski JJ, Belsha CW, Hunley TE, Nelson RD, Trachtman H, Cole TR, Pinsk M, Bockenhauer D, Shenoy M, Vaidyanathan P, Foreman JW, Rasoulpour M, Thameem F, Al-Shahrouri HZ, Radhakrishnan J, Gharavi AG, Goilav B, Lifton RP. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* 2012; 482: 98–102
- Stowasser M, Pimenta E, Gordon RD. Familial or genetic primary aldosteronism and Gordon syndrome. *Endocrinol Metab Clin North Am* 2011; 40: 343–368

- 44 Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM. *Endocrine Society*. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93: 3266–3281
- 45 Hannemann A, Wallaschofski H. Prevalence of primary aldosteronism in patient's cohorts and in population-based studies – a review of the current literature. *Horm Metab Res* 2012; 44: 157–162
- 46 Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med* 2008; 168: 80–85
- 47 Mulatero P, Monticone S, Bertello C, Viola A, Tizzani D, Iannaccone A, Crudo V, Burrello J, Milan A, Rabbia F, Veglio F. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. *J Clin Endocrinol Metab* 2013; 98: 4826–4833
- 48 Preston RA, Materson BJ, Reda DJ, Williams DW, Hamburger RJ, Cushman WC, Anderson RJ. Age-race subgroup compared with renin profile as predictors of blood pressure response to antihypertensive therapy. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *JAMA* 1998; 280: 1168–1172
- 49 Bühler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR. Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. *N Engl J Med* 1972; 287: 1209–1214
- 50 Adlin EV, Marks AD, Channick BJ. Spironolactone and hydrochlorothiazide in essential hypertension. Blood pressure response and plasma renin activity. *Arch Intern Med* 1972; 130: 855–858
- 51 Bühler FR, Burkart F, Lütold BE, Küng M, Marbet G, Pfisterer M. Antihypertensive beta blocking action as related to renin and age: a pharmacologic tool to identify pathogenetic mechanisms in essential hypertension. *Am J Cardiol* 1975; 36: 653–669
- 52 Stumpe KO, Overlack O. Diuretics, beta-blockers or both as treatment for essential hypertension. *Br J Clin Pharmacol* 1979; 7: 189S–197S
- 53 Veterans Administration Co-operative Study Group On Antihypertensive Agents. Racial differences in response to low-dose captopril are abolished by the addition of hydrochlorothiazide. *Br J Clin Pharmacol* 1982; 14: 97S–101S
- 54 Saunders E, Weir MR, Kong BW, Hollifield J, Gray J, Vertes V, Sowers JR, Zemel MB, Curry C, Schoenberger J, Wright JT, Kirkendall W, Conradi EC, Jenkins P, McLean B, Massie B, Berenson G, Flamenbaum W. A comparison of the efficacy and safety of a beta-blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* 1990; 150: 1707–1713
- 55 Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, Gottdiener J, Ramierz EA, Henderson WG for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993; 328: 914–921
- 56 Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; 353: 2008–2013
- 57 Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RS, Brown MJ. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *J Hypertens* 2002; 20: 771–777
- 58 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997
- 59 Gupta AK, Poulter NR, Dobson J, Eldridge S, Cappuccio FP, Caulfield M, Collier D, Cruickshank JK, Sever PS, Feder G, ASCOT. Ethnic differences in blood pressure response to first and second-line antihypertensive therapies in patients randomized in the ASCOT Trial. *Am J Hypertens* 2010; 23: 1023–1030
- 60 Philipp T, Anlauf M, Distler A, Holzgreve H, Michaelis J, Wellek S. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. *HANE Trial Research Group*. *BMJ* 1997; 315: 154–159
- 61 Brown MJ, Cruickshank JK, Dominiczak AF, MacGregor GA, Poulter NR, Russell GI, Thom S, Williams B. Executive Committee, British Hypertension Society. Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003; 17: 81–86
- 62 Vaughan ED Jr, Laragh JH, Gavras I, Bühler FR, Gavras H, Brunner HR, Baer L. Volume factor in low and normal renin essential hypertension. Treatment with either spironolactone or chlorthalidone. *Am J Cardiol* 1973; 32: 523–532
- 63 Laragh JH, Baer L, Brunner HR, Bühler FR, Sealey JE, Vaughan ED Jr. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. *Am J Med* 1972; 52: 633–652
- 64 Laragh JH, Sealey JE. The plasma renin test reveals the contribution of body sodium-volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. *Am J Hypertens* 2011; 24: 1164–1180
- 65 Sealey JE, Parra D, Rosenstein R, Laragh JH. "Effective" plasma renin activity: a derived measure for assessing residual plasma renin activity in patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. *Hypertension* 2010; 55: e16
- 66 Cody RJ, Laragh JH, Case DB, Atlas SA. Renin system activity as a determinant of response to treatment in hypertension and heart failure. *Hypertension* 1983; 5: III36–III42
- 67 Woods JW, Pittman AW, Pulliam CC, Werk EE Jr., Waider W, Allen CA. Renin profiling in hypertension and its use in treatment with propranolol and chlorthalidone. *N Engl J Med* 1976; 294: 1137–1143
- 68 Pedersen EB, Kornerup HJ. Plasma renin concentration in essential hypertension during beta-adrenergic blockade and vasodilator therapy. *Eur J Clin Pharmacol* 1977; 12: 93–96
- 69 Nilsson OR, Karlberg BE, Ohlsson O, Thulin T, Tolagen K. Atenolol administered once daily in primary hypertension. Effects on blood pressure in relation to pre-treatment plasma renin activity. *Acta Med Scand* 1979; 206: 303–308
- 70 Wyndham RN, Gimenez L, Walker WG, Whelton PK, Russell RP. Influence of renin levels on the treatment of essential hypertension with thiazide diuretics. *Arch Intern Med* 1987; 147: 1021–1025
- 71 Weir MR, Saunders E. Renin status does not predict the anti-hypertensive response to angiotensin-converting enzyme inhibition in African-Americans. *Trandolapril Multicenter Study Group*. *J Hum Hypertens* 1998; 12: 189–194
- 72 Minami J, Ishimitsu T, Matsuoka H. Pretreatment plasma renin activity levels correlate with the blood pressure response to telmisartan in essential hypertension. *Am J Hypertens* 2008; 21: 10–13
- 73 Minami J, Ohno E, Furukata S, Ishimitsu T, Matsuoka H. Pretreatment levels of plasma renin activity predict ambulatory blood pressure response to valsartan in essential hypertension. *J Hum Hypertens* 2009; 23: 683–686
- 74 Chrysant SG, Danisa K, Kem DC, Dillard BL, Smith WJ, Frohlich ED. Racial differences in pressure, volume and renin interrelationships in essential hypertension. *Hypertension* 1979; 1: 136–141
- 75 Schwartz GL, Bailey K, Chapman AB, Boerwinkle E, Turner ST. The role of plasma renin activity, age, and race in selecting effective initial drug therapy for hypertension. *Am J Hypertens* 2013; 26: 957–964
- 76 Turner ST, Schwartz GL, Chapman AB, Beitelshes AL, Gums JG, Cooper-DeHoff RM, Boerwinkle E, Johnson JA, Bailey KR. Plasma renin activity predicts blood pressure responses to beta-blocker and thiazide diuretic as monotherapy and add-on therapy for hypertension. *Am J Hypertens* 2010; 23: 1014–1022
- 77 Suonsyrjä T, Hannila-Handelberg T, Paavonen KJ, Miettinen HE, Donner K, Strandberg T, Tikkanen I, Tilvis R, Pentikäinen PJ, Kontula K, Hiltunen TP. Laboratory tests as predictors of the antihypertensive effects of amlodipine, bisoprolol, hydrochlorothiazide and losartan in men: results from the randomized, double-blind, crossover GENRES Study. *J Hypertens* 2008; 26: 1250–1256
- 78 Weintraub HS, Duprez DA, Cushman WC, Zappe DH, Purkayastha D, Samuel R, Izzo JL Jr. Antihypertensive response to thiazide diuretic or angiotensin receptor blocker in elderly hypertensives is not influenced by pretreatment plasma renin activity. *Cardiovasc Drugs Ther* 2012; 26: 145–155
- 79 Leotta G, Rabbia F, Testa E, Totaro S, Abram S, Milan A, Mulatero P, Veglio F. Efficacy of antihypertensive treatment based on plasma renin activity: An open label observational study. *Blood Press* 2010; 19: 218–224
- 80 Egan BM, Basile JN, Rehman SU, Davis PB, Grob CH 3rd, Riehle JF, Walters CA, Lackland DT, Merali C, Sealey JE, Laragh JH. Plasma Renin test-guided treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. *Am J Hypertens* 2009; 22: 792–801
- 81 Blumenfeld JD, Laragh JH. Renin system analysis: a rational method for the diagnosis and treatment of the individual patient with hypertension. *Am J Hypertens* 1998; 11: 894–896

- 82 Smith SM, Campbell JD. Cost-Effectiveness of Renin-Guided Treatment of Hypertension. *Am J Hypertens* 2013; 26: 1303–1310
- 83 Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357
- 84 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Oggedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520
- 85 Williams B, Poulter NR, Brown MJ, Davis M, McNnes GT, Potter JF, Sever PS, McG Thom S, *British Hypertension Society*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; 18: 139–185
- 86 Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens* 2006; 24: 2131–2141
- 87 Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201–207
- 88 ONTARGET Investigators. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559
- 89 *National Institute for Health and Clinical Excellence – National Clinical Guideline Centre*. Clinical Guideline 127. Hypertension – The clinical management of primary hypertension in adults. August 2011. Available at www.nice.org.uk/guidance/CG127 (accessed online on 24th, March 2014)
- 90 Leenen FH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, Alderman MH, Atlas SA, Basile JN, Cuyjet AB, Dart R, Felicetta JV, Grimm RH, Haywood LJ, Jafri SZ, Proschan MA, Thadani U, Whelton PK, Wright JT, *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group*. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2006; 48: 374–384
- 91 Alderman MH, Cohen HW, Sealey JE, Laragh JH. Pressor responses to antihypertensive drug types. *Am J Hypertens* 2010; 23: 1031–1037