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SPECIAL REPORT

Aldosterone-to-renin ratio as a screening test for primary aldosteronism – The Dutch ARRAT Study

P.M. Jansen*, F. Boomsma, A.H. van den Meiracker, the Dutch ARRAT investigators

Department of Internal Medicine, Division of Vascular Pharmacology and Metabolism, Erasmus Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands, *corresponding author: e-mail: p.jansen.1@erasmusmc.nl

ABSTRACT

Since the introduction of the aldosterone-to-renin ratio (ARR) as a screening tool for primary aldosteronism (PA), there has been a marked increase in the reported prevalence of this condition among hypertensive subjects. A meta-analysis from the literature shows a PA prevalence of almost 8% among hypertensive patients, with a twofold higher prevalence in referred patients as compared with primary care patients (9.0 *vs* 4.3%). However, the usefulness of the ARR remains subject of debate, because of doubts on its validity, and the many factors affecting the ARR, including posture, time of day of blood sampling, and use of antihypertensive medication. Furthermore, there is no clear cut-off value and it is unknown what population should be screened. Recently, The Dutch ARRAT Study was initiated. This is a multicentre, prospective trial aiming to evaluate the test characteristics of the ARR within a Dutch population of therapy-resistant hypertensive patients. The effect of antihypertensive medication on the ARR will be studied. Furthermore, from this study the prevalence of PA in this population will follow. Last, the blood pressure response to the selective aldosterone-receptor-antagonist eplerenone will be evaluated. The Dutch ARRAT Study will run until the end of 2009 and will contribute to the formulation of uniform guidelines for the screening for PA in the Netherlands.

KEYWORDS

Aldosterone-to-renin ratio, hypertension, primary aldosteronism

BACKGROUND

Primary aldosteronism (PA) has been a well-known cause of hypertension since the 1950s when Jerôme Conn described a disease state characterised by severe hypertension and hypokalaemia. The cause turned out to be an aldosterone-producing adrenal tumour.[1] Albeit a well-known cause of hypertension, PA was considered to be extremely rare with an estimated prevalence ranging from 0.05 to 2%. This was partly due to the lack of reliable screening tests. The suspicion of PA was mainly raised in the presence of resistant hypertension and hypokalaemia.[2]

Since the introduction of the aldosterone-to-renin ratio (ARR) in 1981,[3] the reported prevalence of PA has increased considerably,[4] and it is nowadays considered a major cause of hypertension by many investigators.

Prevalence studies

Since the introduction of the ARR numerous studies have investigated the prevalence of PA.[5-27] These studies differ in the population that was screened, the screening test that was used and the applied cut-off values of abnormality. Also, there were differences in the diagnostic workup, as will be discussed later. An overview of these studies is given in *table 1,* subdivided into primary care patients (*table 1A*), referred patients with moderate to severe, often poorly controlled hypertension (*table 1B*), and special subgroups (*table 1*C).

The prevalence of an elevated ARR in the reported studies ranged from 0 to 37%, with a weighed mean value of 19%. The prevalence of confirmed PA ranged from 0.7 to 27% with a weighed mean value of 7.8%. The prevalence of PA is highly dependent on the studied population. Rossi *et al.* found an increase in prevalence of PA with increasing severity of hypertension. The mean prevalence in this

Table 1A. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in primary care patients*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
5	Drug trial volunteers with hypertension	52	Australia	Cessation of diuretics	PAC/PRA (3x)	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	12	FST	12	0	33
9	Primary care clinic hypertensive patients	350	Singapore	Unchanged antihypertensive regimen	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	PAC/PRA>20 PAC>15	18	Iv SLT	4.6	38	50
14	Primary care clinic hypertensive patients	609	Chili	Cessation of β-blockers, ACE-I, ARB, diuretics, spironolactone and aspirin	SA/PRA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	10	FST	6.1	2.7	5.4
16	Patients with essential hypertension	118	USA	Unchanged antihypertensive regimen	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	12.4 (ROC curve)	32	Oral SLT	13	NA	0
20	Mild to moderate, normokalaemic hypertensive patients	347	USA	Cessation of all antihypertensive medication	SA/PRA + elevated SA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	SA/PRA > 25 SA > 8	7.5	Oral SLT	3.2	0 (per definition)	NA
22	Primary care hypertensive patients	200	Sweden	Cessation of all antihypertensive medication except calcium blockers	SA/PRC	SA: pmol l^{-1} PRC: ng l^{-1}	100	25	FST	8.5	NA	6.3
25	Randomly selected, primary care hypertensive patients	287	Italy	Cessation of antihypertensive medication except doxazosin and verapamil	PAC/DAR	PAC: pg ml^{-1} DAR: pg ml^{-1}	32	32	-	NA	NA	NA
26	Unselected primary care hypertensive patients	846	UK	Unchanged antihypertensive regimen	PAC/PRA	PAC: pmol l^{-1} PRA: pmol ml^{-1} hr^{-1}	800	14	PAC/PRA >800 + PAC >400 and adrenal adenoma or ΔSBP >20 mmHg on spironolactone	0.7	17	17
Mean								*16*		*4.3*	*12*	*15*

ARR = aldosterone-to-renin ratio; PA = primary aldosteronism; P(ARR) = prevalence of an elevated ARR; P(PA) = prevalence of PA; PAC = plasma aldosterone concentration; SA = serum aldosterone concentration; PRA = plasma renin activity; APA = aldosterone-producing adenoma; DAR = direct active renin; FST = fludrocortisone suppression test; SLT = salt loading test; LDF-score = logistic discriminant function – score; ACE-I = angiotension converting enzyme inhibitors; ARB = angiotensin II receptor blocker; NA = not available; ND = not done. PAC = to convert ng/dl to pmol/l multiply by 27.7. *In patients with an elevated ARR. **The LDF score is explained in Rossi *et al.* (1998).[42] Weighed means for the prevalence of an increased ARR and of PA are based on the total number of cases divided by the total number of patients in the reported studies. Mean percentages of hypokalaemia and APA are weighed for the total number of PA cases in the reported studies.

Table 1B. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in referred patients*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
6	Referred, normokalaemic hypertensive patients	199	Australia	None	PAC/PRA (3x)	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	11	FST	8.5	0 (per definition)	29
7	Unselected hypertension clinic population	465	UK	Cessation of antihypertensive treatment if possible (60 %)	PAC/PRA	PAC: pmol l^{-1} PRA: ng ml^{-1} hr^{-1}	750	17	FST	9.2	4.7	12
8	Hypertension clinic population	305	Chili	No antihypertensive treatment	SA/PRA (2x)	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	14	FST	9.5	0	3.4
10	Referred patients with poorly controlled hypertension	90	USA	Continuation of antihypertensive treatment	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	100	17	ND	NA	40*	67*
11	Referred hypertensive patients	1065	Italy	Cessation of antihypertensive treatment except α-blockers	Post-captopril (50 mg) PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	35	13	iv SLT	6.3	39	24
12	Moderate to severe hypertensive patients	402	Czech Rep.	Cessation of antihypertensive treatment except α-blockers	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	50	22	iv SLT	19	70	36
13	Referred hypertensive patients	300	Australia	Cessation of diuretics, β-blockers, central antihypertensive agents and dihydropyridine calcium blockers	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	20	FST	18	13	31
15	White subjects with resistant hypertension	150	USA	Cessation of spironolactone, triamterene, or amiloride	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	20	32	Oral SLT	20	15	NA
15	African Americans with resistant hypertension	115	USA	Cessation of spironolactone, triamterene, or amiloride	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	20	28	Oral SLT	24		NA
17	Consecutive referred hypertensive patients	1125	Italy	Cessation of antihypertensive medication except calcium blockers and/or doxazosin	SA/PRA	SA: pg ml^{-1} PRA: ng ml^{-1} hr^{-1}	40	19	ARR baseline ≥40 + ARR post captopril ≥30 and/or LDF score ≥50%**	11	30	43
18	Unselected referred hypertensive patients	122	UK	Continuation of antihypertensive treatment	PAC/PRA	PAC: pmol l^{-1} PRA: ng ml^{-1} hr^{-1}	750	16	ND	NA	25*	NA
23	Unselected, consecutive hypertensive patients	3000	Italy	Cessation of all antihypertensive medication and other interfering medication	SA/PRA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	23	iv SLT	5.9	25	30
Mean								20		9.0	29	30

Table 1C. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in special subgroups*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
8	Normotensive control subjects	205	Chili	No antihypertensive treatment	SA/PRA (2x)	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	1.5	FST	1.5	0	0
19	Diabetic patients with hypertension	61	USA	Cessation of spironolactone	PAC/PRA	PAC: ng dl^{-1} PRA: ng dl^{-1} hr^{-1}	30	0	ND	NA	NA	NA
21	Patients with type 2 DM and resistant hypertension	100	USA	None	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	34	Oral SLT (11 %) iv SLT (89 %)	14	NA	NA
24	Normokalaemic hypertensive patients with adrenal incidentalomas	90	Italy	Cessation of antihypertensive medication	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	112	8.8	iv SLT captopril suppression test	5.6	0 (per definition)	40
27	Patients with residual hypertension after successful endovascular treatment of renal artery disease	24	Italy	None	PAC/DAR	PAC: pg ml^{-1} DAR: pg ml^{-1}	23	33.3	iv SLT	27	NA	29

referred population was 11.2%. However, the prevalence ranged from 6.6% in patients with grade I to 19% in grade III hypertension.[17] A similar trend was observed by Mosso *et al*. who found a prevalence of 2.0% in grade I, rising to 13.2% in grade III hypertension.[14] When the mean reported prevalence of PA in primary care patients is compared with referred patients it is clear that it is twice as high in referred patients, who are expected to have more severe hypertension (*figure 1B*). Remarkably, the prevalence of an elevated ARR is almost as high in primary care as in referred patients (*figure 1A*), indicating the higher percentage of false-positive values when applied in a primary care setting. Even in normotensive subjects a small subset appears to have PA, with reported prevalences of around 1.5%.[8,14]

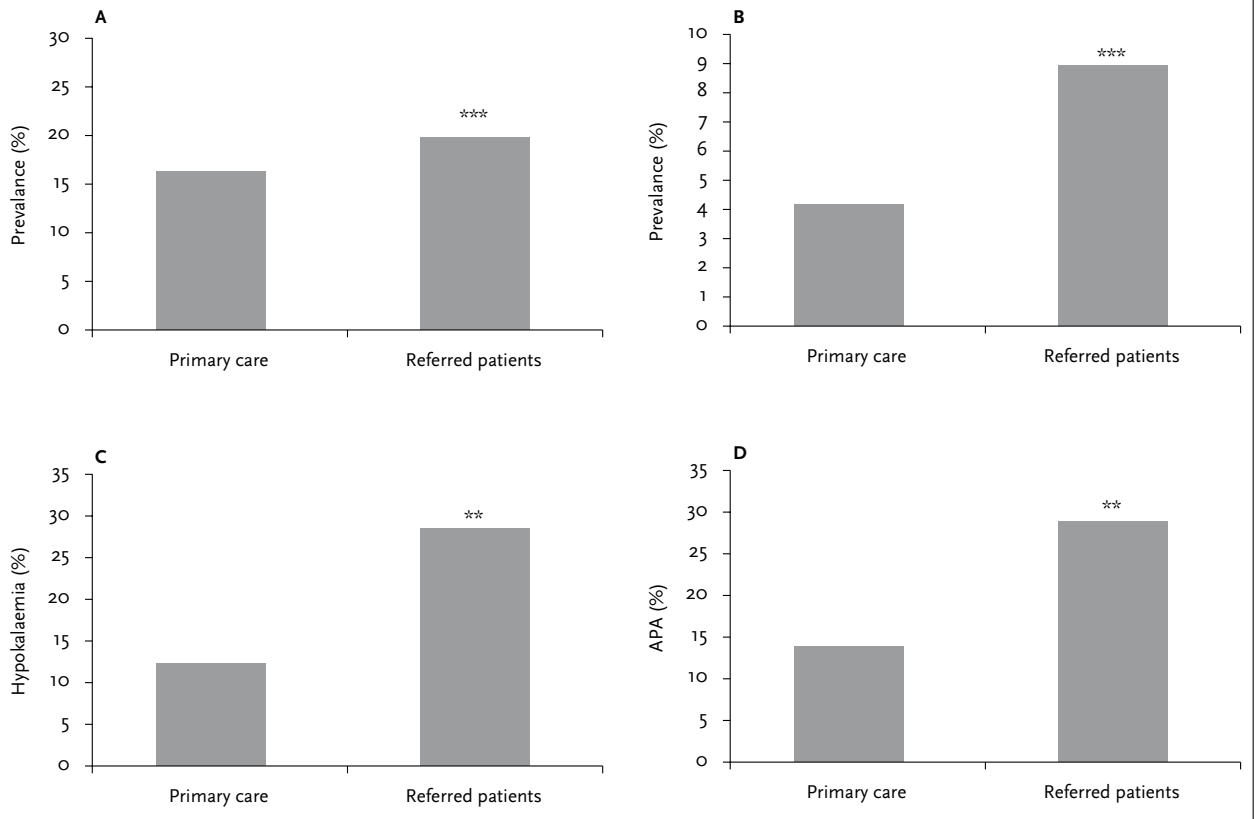
In contrast to former beliefs, many patients with PA present without hypokalaemia, with percentages ranging from 0 to 70%.[5,8-14,17,23,28] In some studies only normokalaemic patients were included.[6,20,24] A retrospective evaluation from centres in five continents showed that between 9 and 37% of patients were hypokalaemic.[4] In the reported studies the percentage of hypokalaemic patients among PA cases was higher in referred patients than in primary care patients (*figure 1C*). Also, the reported numbers of aldosterone-producing adenomas were higher in this group (*figure 1D*). It seems reasonable to conclude that referred patients more frequently have an APA reflected by a more severe phenotype of higher blood pressure levels and lower serum potassium values.

Other subgroups that have been studied for the prevalence of PA include African American patients with resistant hypertension,[15] patients with type 2 diabetes mellitus (DM) and resistant hypertension[21] and hypertensive patients with adrenal incidentalomas.[24] Black subjects generally have lower plasma renin levels than white subjects.[29] However, neither ARR levels nor the prevalence of PA in black and white patients with resistant hypertension were statistically different (24% in African Americans and 20% in white patients).[15,30] In a group of 100 patients with type 2 DM and poorly controlled hypertension a 14% prevalence of PA was reported. This was independent of glycaemic control. This prevalence is similar to reported prevalences in other populations.[21] Patients with adrenal incidentalomas form another group potentially at risk for having PA. Bernini *et al*. screened 90 normokalaemic subjects with an adrenal incidentaloma with hypertension and 35 subjects without hypertension for the presence of PA. Of the subjects with hypertension, 5.6% had PA, whereas no cases were found in the normotensive subgroup, indicating that an adrenal incidentaloma *per se* should not be an indication for screening for PA, unless hypertension is present.[24]

Differences in diagnostic protocols

There are important differences in the diagnostic protocols that were used in the reported studies. The ARR is widely

Figure 1. *Prevalence of A) an elevated aldosterone-to-renin ratio (ARR), B) primary aldosteronism (PA), C) percentage of hypokalaemia and D) aldosterone-producing adenomas (APA) among PA cases in primary care and referred patients*



**p<0.01. ***p<0.001. Figures are based on weighed mean values for the studies reported in *table 1*. The differences are tested using χ^2 testing.

used for screening purposes, but there are variations in the reported cut-off values, depending on the units, and on locally established reference values (*table 1*). Furthermore, in some studies the ARR had to be raised on more occasions for the test to be positive.[5,6,8] Rossi *et al.* assessed ARR after acute administration of captopril, to raise specificity,[11] while other groups included an elevated aldosterone level in the screening test for this purpose.[9,20] In most studies renin was assessed as plasma renin activity (PRA),[5-21,23,24,26] while other studies used plasma renin concentration (PRC).[22,25,27]

Many factors are known to influence the ARR, such as the time of blood sampling and the position of the patient [31,32] and even under standardised conditions biological variability is considerable.[33] These factors account for the wide variation in reported cut-off values making it difficult to formulate a uniform cut-off value.[32] For a correct interpretation of the ARR, sampling conditions should be standardised within and between centres in the same diagnostic setting, using locally established reference values.[32,34]

Some antihypertensive drugs are known to affect aldosterone and renin levels. Beta-blockers cause a decrease in plasma renin levels, thereby leading to an overestimation of the number of positive cases (false-positivity),[35,36] whereas angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers can lead to false-negative results by increasing plasma renin levels.[36] Some protocols required cessation of all antihypertensive drugs[8,20,23,24] whereas other studies allowed the use of certain specific combinations of antihypertensive medications (*table 1*). In some studies no alterations in antihypertensive treatment were made,[9,10,18,21,27] especially when discontinuation of antihypertensive treatment was considered dangerous.[21,27] The most frequently allowed combination of antihypertensive drugs was doxazosin and/or calcium channel blockers.[11-14,17,22,25] Possibly, other factors can be of influence on the ARR as well, for instance the use of non-steroidal anti-inflammatory drugs.[34]

Debate on the ARR as a screening test for PA

Some authors dispute the usefulness of the ARR as a screening test for PA because of the many influencing factors, poor reproducibility, and low sensitivity and specificity.[34,37,38] Furthermore, an elevated ARR may be merely a reflection of low renin levels without indicating

whether there is indeed autonomous secretion of aldosterone, or whether it is mainly a case of 'regular' low-renin hypertension.[31,37,39,40] Also, the clinical relevance of an increased ARR remains unclear.[41] The application of the ARR in an unselected hypertensive population could therefore lead to an enormous increase in costs.[38]

The discussion on the validity of the ARR as a screening test has led to the evaluation of alternative screening methods. Rossi *et al.* have developed a logistic multivariate model in which the probability of PA is calculated based on parameters such as PRA, serum potassium and plasma aldosterone.[42]. Seiler *et al.* have simplified this model to the (serum aldosterone)^2-to-PRA ratio which supposedly has a better diagnostic value than the conventional ARR.[35] However, the validity of this test has not been prospectively evaluated.

Confirmation tests and subtyping

Most authors agree that the ARR should only be used as a screening test and that patients with an elevated ARR should be subjected to a confirmation test to establish the diagnosis. The most frequently applied confirmation tests are the intravenous or oral salt loading test and the fludrocortisone-suppression test.[43]

Most studies include subtyping after establishing the diagnosis of PA. The most important subgroups of PA are aldosterone-producing adenomas (APA) and idiopathic primary aldosteronism (IPA). Glucocorticoid-remediable aldosteronism (GRA) is a genetic form of PA in which crossing-over of the CYP11B1 and CYP11B2 genes leads to a hybrid gene, coding for aldosterone synthase, but under main regulation by ACTH instead of angiotensin II.[44]

In most studies, subtyping was performed using computed tomography (CT) or magnetic resonance imaging (MRI) techniques to visualise any adrenal abnormalities.[5,7,8,10-14,16,23] In some cases adrenal venous sampling (AVS) was used to assess lateralisation of aldosterone production.[5,6,9,12,13] Gallay *et al.* and Rossi *et al.* utilised scintigraphic techniques to detect any functional tumours.[10,11] GRA was mostly detected using a dexamethasone-suppression test or genetic testing. The prevalence of APAs among PA cases is given in *table 1* and ranged from 0 to 67%.

Mulatero *et al.* showed that widespread screening for PA has led to a shift in the proportion of bilateral hyperplasia as a cause of PA, with this subtype now comprising the majority of cases. Interestingly, the detection rate of APAs appears to be mainly dependent on the availability of AVS, with higher proportions found in centres where AVS was available.[4,17] This supports the superiority of AVS to detect lateralised aldosterone production over CT or MRI. This has been confirmed by Stowasser *et al.* who found a large incoherence between the findings in radiological imaging *vs* AVS.[13]

CONCLUSION

PA appears to be a relatively frequent cause of hypertension, with prevalences ranging up to more than 20%, depending on the population subjected to screening. Most cases present without hypokalaemia. Furthermore, diagnostic protocols vary in their individual steps and methods. Several known and unknown factors can influence the ARR.

Diagnosing PA as a cause of hypertension is important. First, because patients with PA have more cardiovascular events than patients with essential hypertension, independent of blood pressure, stressing the need for early detection to prevent complications.[45] Second, because specific treatment is available: adrenalectomy in case of an adrenal adenoma and treatment with an aldosterone-receptor-antagonist in case of bilateral adrenal hyperplasia.[46,47]

The Dutch ARRAT Study

Because of the discussion concerning the correct diagnostic pathway for the screening for PA, a study on the diagnostic value of the ARR for the Dutch situation is needed. This has led to the design of The Dutch ARRAT Study.

The Dutch ARRAT Study is a prospective, multicentre study, in which the diagnostic value of the ARR and the prevalence of PA will be evaluated within a Dutch population of therapy-resistant hypertensive patients. Furthermore, the effect of add-on therapy with an aldosterone-receptor antagonist on blood pressure will be studied.

The objectives of The Dutch ARRAT Study are outlined in *table 2*.

The inclusion and exclusion criteria for the study population are given in *table 3*. It is planned to include a total of 500 patients over a period of three years. Nineteen centres will participate.

Patients will be followed-up for a period of 35 weeks. Before inclusion β-blocking agents and potassium-sparing diuretics are stopped. In the first stage reproducibility of the ARR will be studied. As gold standard for the presence or absence of PA an intravenous salt loading test will be performed. Also, an oral salt loading test will be done to assess the validity of this less cumbersome test. During the intravenous salt loading test plasma aldosterone levels

Table 2. *Objectives of The Dutch ARRAT Study*

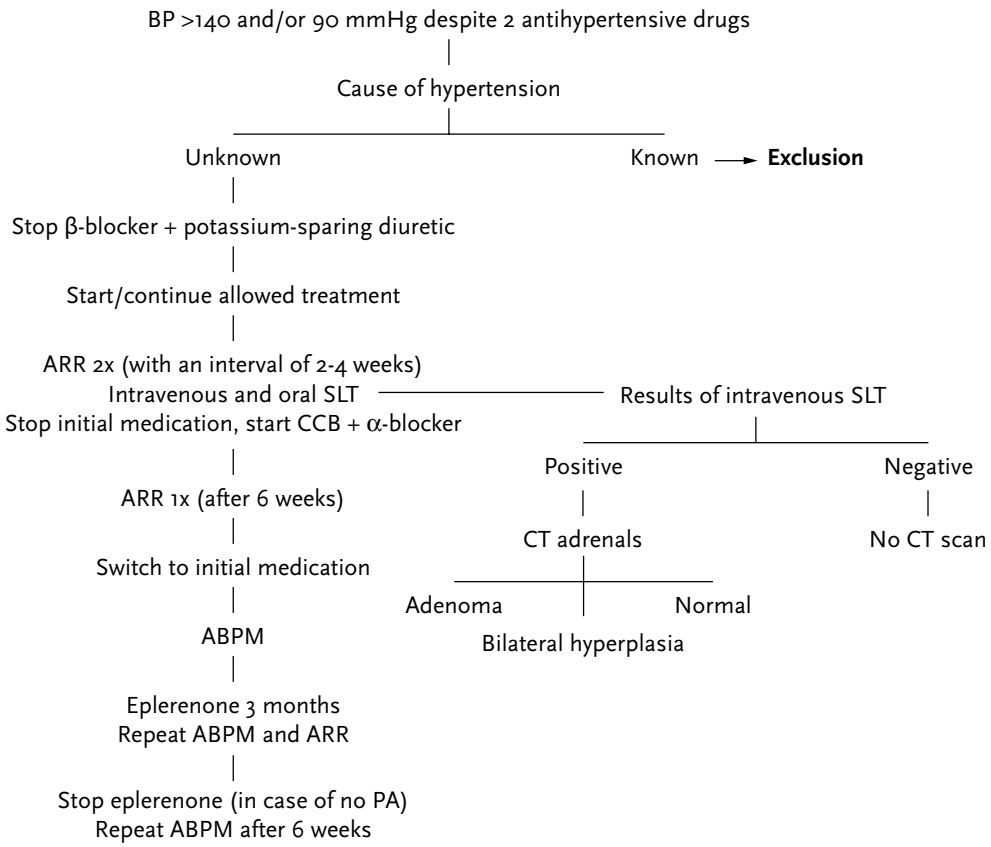
Evaluation of the test characteristics of the aldosterone-to-renin ratio
Evaluation of the effect of antihypertensive medication on the aldosterone-to-renin ratio
Assessment of the prevalence of primary aldosteronism in a Dutch population of patients with therapy-resistant hypertension
Evaluation of the clinical response to an aldosterone-receptor antagonist in this population

Table 3. *Inclusion and exclusion criteria of The Dutch ARRAT Study*

Inclusion criteria
Age 18-65 years
Office blood pressure >140 mmHg systolic and/or >90 mmHg diastolic or ambulant blood pressure >135 mmHg systolic and/or >85 mmHg diastolic
Use of an effective combination of at least two antihypertensive drugs
Exclusion criteria
Known cause of hypertension
White-coat hypertension
Serum creatinine level >200 µmol/l
Body mass index >32 kg/m^2
Poorly regulated diabetes mellitus (HbA_1C >8.0%)
Heart failure
Stroke, transient ischaemic attack or myocardial infarction in the past 6 months
Angina pectoris
Pregnancy
Neoplastic disease in the past 5 years
Alcohol abuse

will be assessed before and after a four-hour infusion of two litres of physiological salt solution. During the oral salt loading test the 24-hour urinary aldosterone excretion will be assessed while the patient is on a sodium-rich diet. In both tests an insufficient suppression of aldosterone is diagnostic of PA. For the intravenous salt loading test this is defined as a post-infusion plasma aldosterone exceeding 85 pg/ml and for the oral salt loading test as a 24-hour urinary aldosterone excretion exceeding 12 µg. Then, in all patients their original antihypertensive medications will be replaced by standardised medication consisting of doxazosin and amlodipine. After six weeks the ARR will be tested again. After restarting their own antihypertensive drugs, the effect of add-on therapy with eplerenone, a selective aldosterone-receptor-antagonist, on blood pressure and ARR will be evaluated. The blood pressure response will be evaluated with 24-hour ambulant blood pressure monitoring devices (ABPM). If the salt loading test is indicative for PA, a CT scan of the adrenal glands will be performed to assess the subtype of PA (adrenal adenoma or bilateral adrenal hyperplasia). The protocol is summarised in *figure 2*.

Figure 2. *Flowchart of The Dutch ARRAT Study*



BP = blood pressure; ARR = aldosterone-to-renin ratio; SLT = salt loading test; CCB = calcium-channel blocker; ABPM = ambulant blood pressure measurement; CT = computed tomography; PA = primary aldosteronism.

Time schedule

The inclusion started in December 2006. At the moment of writing, 50 patients have been included in the study protocol. Most centres have not yet started inclusion. Data collection will run until the end of 2009.

Expected outcomes

The Dutch ARRAT Study will provide data on the test characteristics and determinants of the ARR, the prevalence of PA in therapy-resistant hypertensive patients from the Dutch population and determinants of the clinical response to an aldosterone-receptor antagonist in this selected population. These data will ultimately contribute to the formulation of uniform guidelines for the diagnosis of primary aldosteronism in the Netherlands.

For more information about the study the authors can be contacted, also if you are interested in participating. If you have a patient meeting the criteria for inclusion, referral to one of the participating centres can be considered.

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