

A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

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OBJECTIVES	We prospectively investigated the prevalence of curable forms of primary aldosteronism (PA) in newly diagnosed hypertensive patients.
BACKGROUND	The prevalence of curable forms of PA is currently unknown, although retrospective data suggest that it is not as low as commonly perceived.
METHODS	Consecutive hypertensive patients referred to 14 hypertension centers underwent a diagnostic protocol composed of measurement of Na ⁺ and K ⁺ in serum and 24-h urine, sitting plasma renin activity, and aldosterone at baseline and after 50 mg captopril. The patients with an aldosterone/renin ratio >40 at baseline, and/or >30 after captopril, and/or a probability of PA (by a logistic discriminant function) ≥50% underwent imaging tests and adrenal vein sampling (AVS) or adrenocortical scintigraphy to identify the underlying adrenal pathology. An aldosterone-producing adenoma (APA) was diagnosed in patients who in addition to excess autonomous aldosterone secretion showed: 1) lateralized aldosterone secretion at AVS or adrenocortical scintigraphy, 2) adenoma at surgery and pathology, and 3) a blood pressure decrease after adrenalectomy. Evidence of excess autonomous aldosterone secretion without such criteria led to a diagnosis of idiopathic hyperaldosteronism (IHA).
RESULTS	A total of 1,180 patients (age 46 ± 12 years) were enrolled; a conclusive diagnosis was attained in 1,125 (95.3%). Of these, 54 (4.8%) had an APA and 72 (6.4%) had an IHA. There were more APA (62.5%) and fewer IHA cases (37.5%) at centers where AVS was available (p = 0.002); the opposite occurred where AVS was unavailable.
CONCLUSIONS	In newly diagnosed hypertensive patients referred to hypertension centers, the prevalence of APA is high (4.8%). The availability of AVS is essential for an accurate identification of the adrenocortical pathologies underlying PA. (J Am Coll Cardiol 2006;48:2293–300) © 2006 by the American College of Cardiology Foundation

Primary aldosteronism (PA) is a common cause of arterial hypertension (HT); however, more than 50 years after its discovery (1) its prevalence in newly diagnosed hypertensive patients remains uncertain. A survey of 18 recent studies showed a wide range (from 1.4% to 32%, median 8.8%) of estimates of prevalence (2). This is because most studies were performed retrospectively in a selected cohort of patients and used heterogeneous criteria for selecting the patients and diagnosing PA (3–15). Importantly, it should also be acknowledged that PA can only be conclusively diagnosed in the patients who are cured or improved by removal of an aldosterone-producing adenoma (APA) or unilateral adrenal hyperplasia (16). The other major PA subtype, idiopathic hyperaldosteronism (IHA), should not

be treated surgically and therefore cannot stand on this retrospective criterion. Furthermore, differentiation of IHA from low-renin primary (essential) HT is arbitrary (7,17). Thus, establishing the prevalence of PA is a challenging task, which requires: 1) the prospective investigation of newly diagnosed consecutive unselected hypertensive patients, 2) the use of predefined state-of-the-art diagnostic criteria, and 3) an unequivocal diagnosis that is feasible only retrospectively in APA treated with adrenalectomy. A study of the unselected hypertensive patients, seen by general practitioners, is hard to perform and to justify for cost-effectiveness reasons; furthermore, it can be hampered by the difficulty of achieving a conclusive diagnosis of PA and of its underlying cause, which requires the expertise and facilities that are usually available only at specialized centers. The only attempt in this direction best testifies this difficulty because it furnished data only on the prevalence of an elevated aldosterone/renin ratio (ARR) and not of PA (18).

For a list of author affiliations, please see the Appendix. Supported by grants from FORICA (The Foundation for Advanced Research in Hypertension and Cardiovascular Diseases) to Dr. Rossi and from the Società Italiana dell'Ipertensione Arteriosa.

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Abbreviations and Acronyms

APA = aldosterone-producing adenoma
ARR = aldosterone/renin ratio
AVS = adrenal vein sampling
CT = computed tomography
HT = hypertension
IHA = idiopathic hyperaldosteronism
LDF = logistic discriminant analysis
MR = magnetic resonance
PA = primary aldosteronism
PRA = plasma renin activity

A large-scale multicenter study carried out prospectively at referral centers could minimize the chances of selection biases and furnish firm evidence on the accuracy of diagnostic tests for PA (19). Hence, at the end of 2001 a Working Group of the Italian Society of Arterial Hypertension started nationwide a prospective survey aimed at determining the prevalence of APA in newly diagnosed hypertensive patients referred to specialized centers for HT in Italy. This article reports on the main results of this investigation that was named the PAPY (PA Prevalence in Hypertensives) study, whereas data on early renal involvement have been reported elsewhere (20).

METHODS

Overview. The study design followed the recommendations of the STARD (Statement for Reporting Studies of Diagnostic Accuracy) (21). The protocol (Fig. 1) was approved by the ethical committee of the University of Padua, and an informed written consent was obtained from each participant. To minimize the chance of any selection bias, it was decided a priori to enroll consecutive patients with a new (within the previous 6 months) diagnosis of HT who had been referred by their family doctor to specialized centers for the diagnosis and treatment of HT nationwide in Italy. A prior diagnosis of any secondary forms of HT and the patient's refusal to participate in the study were exclusion criteria. To ensure homogeneity across centers, it was decided a priori to exclude from the analysis centers that eventually would have recruited fewer than 20 patients.

Screening test. Patients were enrolled after the diagnosis of HT was confirmed by established criteria based on office blood pressure measurement by mercury sphygmomanometer (22). The patients had to be prepared for the screening test as follows: treatment with spironolactone, canrenone, or potassium canrenoate was withdrawn for at least 6 weeks (Fig. 1). Other agents, including diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin

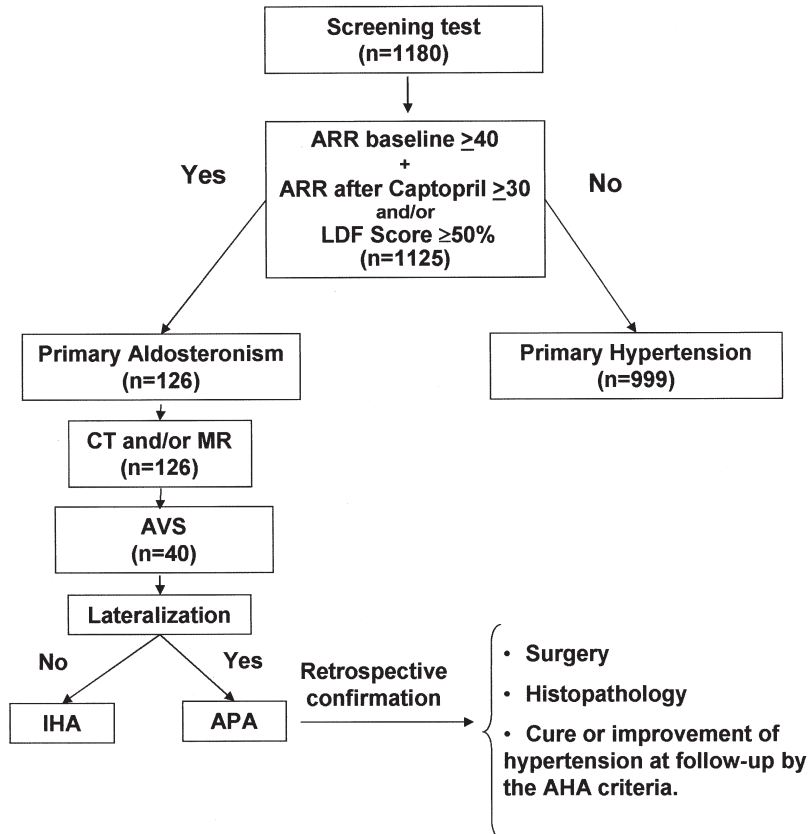


Figure 1. This flowchart shows the protocol for the recruitment and investigation of the PAPY (PA Prevalence in Hypertensives) study population. AHA = American Heart Association; APA = aldosterone-producing adenoma; ARR = aldosterone/renin ratio; AVS = adrenal vein sampling; CT = computed tomography; IHA = idiopathic hyperaldosteronism; LDF = logistic discriminant analysis; MR = magnetic resonance.

II type 1 (AT-1) receptor antagonists, were withdrawn for at least 2 weeks. A long-acting calcium channel blocker and/or doxazosin were allowed as treatment whenever necessary for minimizing the risks of uncontrolled HT. On the day of the test, Na⁺ and K⁺ excretion was measured by 24-h urine collection. The completeness of the urine collection was verified with measurement of urinary creatinine excretion.

After an overnight fast and 1 h quiet rest in the sitting position, between 7 AM and 9 AM the Na⁺ and K⁺, plasma renin activity (PRA), aldosterone, and cortisol were measured at baseline and again 60 min after captopril administration (50 mg orally). The blood pressure levels were measured at baseline and after captopril as previously described.

The aldosterone (in ng/dl)/PRA (in ng/ml/h) ratio, at baseline and after captopril, and a score estimating the probability of PA based on a validated multivariate logistic discriminant analysis (LDF) score (7) were calculated.

Additional tests. A saline infusion test (2 l saline over 4 h with the patients kept in the supine position) (23), with measurement of PRA, aldosterone, cortisol, and serum K⁺ at baseline and again after the infusion, was performed in all patients with: 1) an ARR \geq 40 baseline, and/or 2) an ARR \geq 30 after captopril (24), and/or 3) an LDF score \geq 0.50; as well as 1 in every 4 patients not meeting such criteria. The need for further testing was decided based on the ARR at baseline and the captopril test results, regardless of the saline test results. It was decided that this test should not affect the further diagnostic workup to avoid any bias in the evaluation of the performance of the saline as a confirmatory test for PA.

A high-resolution computed tomography (CT) scan with 3-mm slices and systematic use of a contrast medium, and/or magnetic resonance (MR) imaging, was required in all patients with an ARR \geq 40 baseline and an ARR \geq 30 after captopril, or an LDF score \geq 0.50. The adrenal nodular enlargements, identified with CT and/or MR imaging, were classified by diameter into 3 classes: <10 mm, 11 to 20 mm, and >20 mm. The kappa value between radiologists in classifying these lesions was 0.954 ($p < 0.001$). At the centers where adrenal vein sampling (AVS) (25) was available, it was performed in all of those selected for CT and/or MR as previously described. Dexamethasone-suppressed adrenocortical scintigraphy (26) was used to show a lateralized aldosterone excess production whenever AVS was unavailable. The AVS was performed without ACTH stimulation because the latter was shown not to improve the diagnostic accuracy (27). Only bilaterally selective AVS were judged to provide an accurate diagnosis. The criteria for considering AVS selective and for lateralization of aldosterone secretion were previously established as described in detail (25).

Biochemical measurements. The utmost care was taken in drawing blood by avoiding a tourniquet, fist clenching, and any condition that might artificially increase serum K⁺ (28).

The Na⁺ and K⁺ levels were measured in serum and urine by the standard method; hypokalemia was defined as serum K⁺ \leq 3.5 mEq/l. The glomerular filtration rate was measured using the abbreviated equation (29). Plasma renin activity was measured by radioimmunoassay with commercial kits (Ren CTK, Sorin Biomedica Saluggia, Italy, in 10 centers; or Angiotensin I RIA CT, Radim, Pomezia, Italy, in the remainder). For both kits, the intra-assay and interassay coefficient of variation was within 8% and 10%. Normal range sitting, at rest, and on a normal Na⁺ diet was 0.65 to 2.64 ng/ml/h. The assay for aldosterone was performed with a commercial kit (Aldosterone Mirya, Techogenetics, Cassina de Pecchi, Italy). Normal range was 10 to 150 pg/ml supine and 30 to 320 pg/ml upright on a normal Na⁺ diet; both intra-assay and interassay coefficients of variation for this assay were $<$ 5.6%; the cross-reactivity of the antibody for aldosterone for the other adrenal steroids was $<$ 0.001%. Cortisol was measured with a commercial kit (Cortisol bridge, Adaltis, Casalecchio di Reno, Italy); the intra-assay and interassay coefficients of variation for this assay were below 6% and 10%, respectively. The cross-reactivity of the antibody for steroids was negligible. A survey of hormone values shows no differences across centers; sample centralization in a single laboratory (Padua) for a quality control project is ongoing.

Diagnostic criteria. The Working Group reached the consensus that a positive result of the ARR baseline had to be corroborated by the result of the captopril test. Hence, the diagnosis of PA required evidence of autonomous excess aldosterone production, which was defined as an ARR \geq 40 at baseline plus an ARR \geq 30 after captopril, or a logistic discriminant function \geq 0.50 (7,24). For the calculation of the ARR the PRA values $<$ 0.2 ng/ml/h were arbitrarily set to 0.2. On completion of the diagnostic workup described in Figure 1, an Adjudication Committee (G.P.R., F.M.) was responsible for determining whether patients had PA or not. Moreover, the diagnosis of APA required the following strict predefined criteria: 1) lateralization of aldosterone secretion at AVS, or evidence of lateralized uptake of ¹³¹I-norcholesterol at dexamethasone-suppressed adrenocortical scintigraphy, 2) surgery, 3) pathology, and more importantly, 4) outcome of adrenalectomy as assessed at follow-up. To this end, we required demonstration of normokalemia and cure or improvement of HT at least 120 days after adrenalectomy according to the American Heart Association criteria for evaluation of outcome after correction of renal ischemia (30). Cure was defined as a systolic blood pressure $<$ 140 mm Hg and diastolic blood pressure $<$ 90 mm Hg without medications, and improvement as a systolic and diastolic blood pressure $<$ 140/90 mm Hg, respectively, on the same or a reduced number of medications and/or a reduced number of defined daily doses (31). By exclusion, patients with a biochemical diagnosis of PA without evidence for a lateralized aldosterone excess were held to have IHA.

Statistical analysis. Quantitative variables were first tested for normal distribution, and transformations were undertaken for variables that showed a skewed distribution until a normal distribution was attained. One-way ANOVA followed by a Bonferroni test was used to compare quantitative variables between groups. The distribution of categorical variables was investigated by chi-square analysis. Significance was set at $p < 0.05$.

The sensitivity, specificity, and accuracy of each test were calculated (32). The diagnostic odds ratio, that is the odds of positivity among diseased patients divided by the odds of positivity among nondiseased patients, was also used as measure of the diagnostic accuracy (19). When a test provides no diagnostic evidence, the diagnostic odds ratio is 1.0. The area under the receiver operator characteristics curve was also used to measure and compare the accuracy of the tests (32), for example, serum K^+ , ratio of urinary K^+ excretion to serum K^+ , ARR at baseline and after captopril, and the logistic discriminant function score, for prediction of the conclusive diagnosis of PA or no PA. This strategy was also used to determine the cutoff values that provided the best combination of sensitivity and false-positive rate for each test. The MedCalc software (version 8.1.1.0, MedCalc Software, Mariakerke, Belgium) was used for these purposes.

RESULTS

Clinical and demographic features. On locking the database on September 30, 2004, 4 of the 18 centers had enrolled fewer than 20 patients, and therefore were excluded from the analysis. An additional 17 patients who did not have complete hormone data or showed some violation of the protocol were excluded. Thus, overall 1,180 patients were available for the analysis; their baseline data are shown in Table 1. The comparison of patients with and without

PA showed not only the expected differences of PRA, aldosterone, and serum K^+ , but also an older age and a higher blood pressure in the PA group.

At the time of the screening test, 40% of the patients were untreated, 42% were on a calcium channel blocker or doxazosin, and 18% were on both agents. No patients experienced any problem while untreated, and no untoward effect occurred with captopril administration. There were no significant differences of PRA, aldosterone, and cortisol in either the entire group or PA or the PH patients across treatment groups, thus ruling out any systematic effect of these treatments on the results of the screening test (33,34). Likewise, there were no differences in PRA, aldosterone, and cortisol across centers, thus making unlikely a center effect on hormonal data.

Conclusive diagnosis. At the time of the database locking, 53 patients had not completed the entire diagnostic workup; therefore, a conclusive diagnosis was attained in 95.3% ($n = 1,125$) of the 1,180 patients. On completion of the diagnostic workup (Fig. 1), 126 patients were diagnosed with PA. Therefore, overall the prevalence of the disease was 11.2%, without gender differences (11.7% in men, 10.6% in women). By the aforementioned criteria, an APA was the cause of PA in 54 patients (42.8%), and IHA in the remaining 72 (57.2%). Heterogeneity in the proportion of the underlying adrenal pathologies ($p < 0.001$) across centers was observed. When the 2 centers with the highest prevalence that contributed most to this heterogeneity were excluded, the overall prevalence of PA and APA was 7.4% and 3.5%, respectively.

Screening test. Overall 20.4% of the patients tested positive by at least 1 of the indexes derived from the baseline evaluation and the captopril test by the prespecified criteria (7,24). Table 2 shows the sensitivity, specificity, accuracy, and diagnostic odds ratio (19) of each test at the prespecified

Table 1. Demographic Characteristic of the Patients ($n = 1,125$) Enrolled in the PAPY Study Who Had a Conclusive Diagnosis

Variable	PA ($n = 126$)	Non-PA ($n = 999$)	p Value
Gender (male/female), % (range)	74/52 (59:41)	560/439 (56:44)	
Age (yrs)	49.7 \pm 12.2	45.9 \pm 12.0	0.03
Body mass index	27.4 \pm 4.5	26.9 \pm 4.6	NS
Systolic BP (mm Hg)	155 \pm 19	147 \pm 17	0.0001
Diastolic BP (mm Hg)	98 \pm 11	95 \pm 10	0.0001
HR (beats/min)	72 \pm 9	72 \pm 10	NS
Serum K^+ (mmol/l)	3.6 (2.2-4.7)	4.0 (2.6-5.5)	0.0001
Serum Na^+ (mmol/l)	141 (134-150)	141 (130-152)	NS
Urinary K^+ (mmol/24 h)	59 (13-162)	61 (12-367)	NS
Urinary Na^+ (mmol/24 h)	137 (16-412)	160 (15-826)	0.02
Glomerular filtration rate (ml/min)	84 \pm 17	86 \pm 20	NS
sPRA ($ng \cdot ml^{-1} \cdot h^{-1}$)	0.62 (0.02-0.96)	1.66 (0.2-43.5)	0.0001
s-Aldosterone (pg/ml)	297 (170-2,260)	116 (10-248)	0.0001
s-Cortisol (ng/ml)	135 (5-309)	143 (11-520)	NS

Data are mean \pm SEM; except for serum and urinary K, serum and urinary Na, s-aldosterone, s-PRA, and s-cortisol, for which median (range) are shown. Normal values for s-aldosterone: 20-150 pg/ml; s-PRA: 0.51-2.64 ng/ml/h; s-cortisol: 50-250 ng/ml.

BP = blood pressure; HR = heart rate; K^+ = potassium level; Na^+ = sodium level; PA = primary aldosteronism; s-Aldosterone = sitting plasma aldosterone; s-PRA = sitting plasma renin activity.

Table 2. Sensitivity, Specificity, Overall Accuracy, and Diagnostic Odds Ratio of Each Test at the Prespecified Cutoffs

Variable	Sensitivity (%)	Specificity (%)	Accuracy (%)	DOR
ARR \geq 40 baseline	68	87	92	14.1
ARR \geq 30 captopril	59	91	94	14.6
LDF score \geq 50	91	80	87	42.5

The diagnostic odds ratio (DOR), calculated as the odds of positivity among diseased persons divided by the odds of positivity among nondiseased persons, provides an overall measure of the diagnostic accuracy (19). When a test provides no diagnostic evidence, the DOR is 1.0.

ARR = aldosterone (ng/dl)/renin (ng/ml/h) ratio; LDF = logistic discriminant analysis.

cutoffs. Thus, the screening tests allowed selection of subgroups of hypertensive patients with a higher prevalence of PA. Of the indexes based on the captopril test, the ARR after captopril had a lower sensitivity and a higher specificity than the ARR at baseline, whereas the opposite occurred for the LDF score. The latter showed the highest sensitivity, and therefore the highest diagnostic odds ratio.

Additional tests. The comparison of the diagnostic performances of the saline suppression test and the captopril test for confirming the diagnosis of PA will be reported elsewhere.

Based on the maximum tumor diameter at CT and MR, 17% of the APA was <10 mm diameter; 28% between 10 and 20 mm; and 55% >20 mm.

Prevalence of hypokalemia by conclusive diagnosis. Spontaneous hypokalemia was found in 9.6% of the patients; however, it was observed in about one-half of the patients with APA and only 17% of those with IHA (Fig. 2).

Severity of arterial HT by conclusive diagnosis. Figure 3 shows the prevalence of APA and IHA in the patients classified by blood pressure values at the screening test. High-normal blood pressure (because of ongoing treatment) was seen in about 12% of the patients; despite ongoing treatment 43% of the patients had grade 1, 31% grade 2, and 13.7% grade 3 HT (22). Increasing severity of HT was

associated with an increased prevalence of both APA and IHA (chi-square = 31.4, $p < 0.0001$).

Receiver-operating characteristic curve analysis. By receiver-operating characteristic curve analysis, the accuracy of the ratio of 24-h urinary K^+ excretion to serum K^+ did not differ from 0.5, whereas those for ARR at baseline and after captopril and the logistic discriminant function score were significantly higher (see online supplemental table). The logistic discriminant function score showed the highest accuracy, followed by the ARR after captopril, and the ARR at baseline, which all performed better ($p < 0.0001$) than serum K^+ . The online supplemental table shows that the cutoff values that provided the best tradeoff of sensitivity and specificity for each test differed from those prespecified based on retrospective studies (14,35).

Impact of AVS on subtypes of PA. The AVS was available at 5 of the 14 centers that qualified for the study and was performed in 43 patients; however, it was bilaterally selective in 40 (93%) of the patients. Hence, the hypothesis that the availability of AVS affects the prevalence of adrenocortical pathologies underlying PA could be tested by splitting the centers into those with and those without AVS. We found that at the centers with AVS significantly more cases of APA and fewer cases of IHA were diagnosed

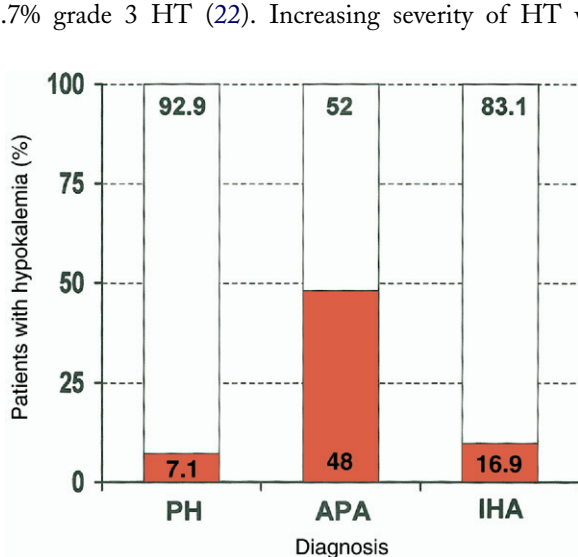


Figure 2. This bar graph shows that a substantial proportion of the patients with APA and IHA did not have hypokalemia (red bars) at the time of presentation. APA = aldosterone-producing adenoma; IHA = idiopathic hyperaldosteronism; PH = primary hypertension.

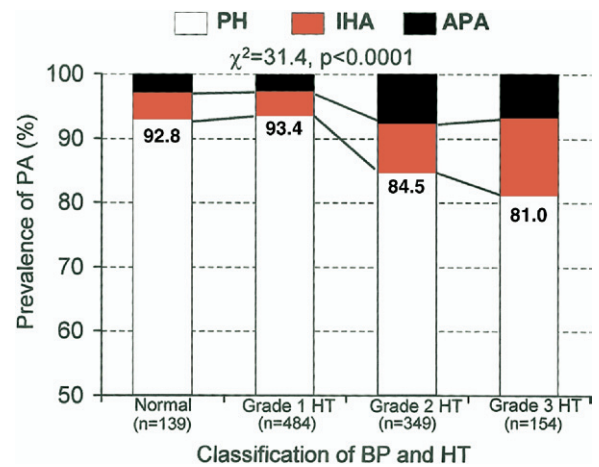


Figure 3. This bar graph shows the proportion of patients without PA (white bars), with IHA (red bars), and with APA (black bars) in the patients at the screening test. The proportion of patients with PA caused by both APA and IHA increased significantly (from 7.2% to 19.5%) with the increasing severity of hypertension. APA = aldosterone-producing adenoma; BP = blood pressure; HT = hypertension; IHA = idiopathic hyperaldosteronism; PA = primary aldosteronism; PH = primary hypertension.

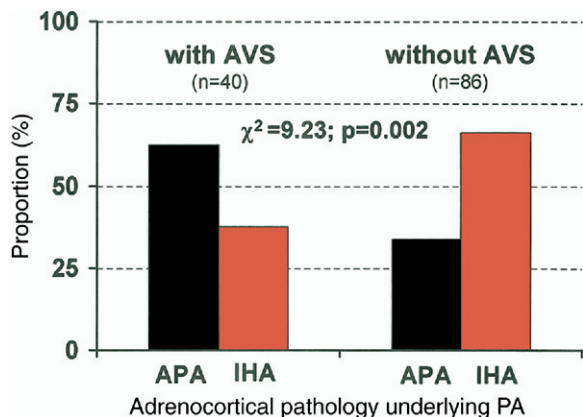


Figure 4. This histogram shows the proportion of PA patients with APA (black bars) and IHA (red bars) by availability of adrenal vein sampling (AVS) in the participating centers. APA = aldosterone-producing adenoma; IHA = idiopathic hyperaldosteronism; PA = primary aldosteronism.

(Fig. 4). The opposite occurred at the centers where AVS was unavailable.

DISCUSSION

Compelling evidence indicates that hyperaldosteronism is associated with detrimental consequences on the cardiovascular system (36), including early renal damage (20). Removal of an APA or a unilateral autonomous hyperplasia normalizes aldosterone secretion, and warrants cure or marked amelioration of HT, and the cardiovascular changes in most patients (37). The systematic search for PA and efforts toward identifying unilateral causes of aldosterone secretion could therefore be justified, particularly if the prevalence of PA were high as suggested (2–15,38), although the cost effectiveness of this strategy has been challenged (39).

This multicenter study prospectively investigated the prevalence of APA and PA with a predefined diagnostic protocol in newly diagnosed hypertensive patients referred to specialized centers for HT nationwide. State-of-the-art tests (40) and a consensus protocol for diagnosing APA were exploited, thus allowing a conclusive establishment of the presence or absence of the disease. Because of these unique features, robust evidence on the prevalence of this potentially curable form of arterial HT and information that may affect future strategies for the screening and diagnosing PA and its underlying causes could be obtained.

Prevalence of PA. Only APA can be unequivocally diagnosed with strict criteria such as those described; at variance, no such diagnostic gold standard exists for identifying IHA (7,17). Thus, although we found that the overall prevalence of PA was 11.2%, which accords well with an earlier prediction (3,5), we would like to underline that an APA was found in 42% of the cases initially held to have PA. Thus, 4.4% of the 1,180 consecutive hypertensive patients originally screened (and 4.6% of those with a conclusive

diagnosis) had an APA that was surgically removed with a long-term cure. This figure might underestimate the proportion of APA for several reasons. First, because we used a rather high ARR baseline for the initial screening, which can provide a higher specificity but a lower sensitivity than lower cutoffs, some PA patients might have been missed. Second, we unexpectedly found a high rate of spontaneous hypokalemia in the patients without PA. Because hypokalemia lowers aldosterone secretion, some of these patients might have had falsely normal aldosterone, which might have been revealed if they had been studied when normokalemic. A few of them might also have apparent mineralocorticoid excess, Liddle syndrome, familial type I hyperaldosteronism (glucocorticoid-remediable aldosteronism), or another undefined cause of primary HT with hypokalemia. Unfortunately, in this multicenter study we had no opportunity to reinvestigate these patients after correction of the hypokalemia and to dissect these monogenetic forms of HT. Finally, at centers where AVS was unavailable, IHA was diagnosed by exclusion of an APA. As discussed later, the tests used as an alternative to AVS (CT or MR and dexamethasone-suppressed adrenocortical scintigraphy) are inaccurate for diagnosing a small APA, thus suggesting that some APAs have been missed at these centers.

Generalizability of the results. Our patients were referred to a specialized HT center. We found a heterogeneity of PA prevalence across centers, which suggests occurrence of some referral bias despite all of the precautions that were taken. The relevance of our results to the practicing generalist evaluating patients with HT may therefore be questioned. The following considerations, however, are necessary. First, patients were enrolled consecutively without applying any selection criteria (such as serum K⁺, blood pressure levels, and/or resistance to the antihypertensive treatment). Second, patients who had any clues to a secondary form of HT were carefully excluded. Third, the anthropometric and blood pressure data (Table 1) are similar to those of the general Italian population of hypertensive individuals. Fourth, the prevalence of a high ARR in this study was even lower than the 32.4% prevalence of a high ARR found in a general practitioners study in Italy, despite the use of a higher (>50) cutoff (18). Finally, even after the exclusion of the centers with the highest prevalence of PA, the rate of APA remained around 3.5%. Thus, while retaining general validity, our data support the view that the screening for PA in the newly diagnosed hypertensive patients is justified and can open the door to a cure of arterial HT in several cases.

Screening tests. We calculated the ARR at baseline and 2 additional indexes, the ARR after captopril and the logistic discriminant function score, that are viewed as confirmatory tests (40). These indexes outperformed spontaneous hypokalemia and the ratio of 24-h urinary K⁺ excretion to serum K⁺ when compared by receiver-operating characteristic

curve analysis (see online supplemental table). This was because a substantial proportion of our patients without PA had hypokalemia and conversely, most patients with confirmed PA had normokalemia (Fig. 2). Thus, nowadays the normokalemic cases of PA seem to be the rule rather than the exception, in accord with most studies (7,41), albeit not all of the retrospective studies (10). The widespread use of low-sodium and/or high-potassium diets along with the more diffuse prescription of potassium-sparing antihypertensive drugs, such as angiotensin-converting enzyme inhibitors and AT-1 receptor antagonists, which were not permitted in this study, are likely explanations for the current common occurrence of normokalemic cases of PA. Clinically, this result implies that if hypokalemia were to be used as a screening test, the majority of the PAs would have been missed (7,14,40,41).

Tests for identifying the underlying adrenal pathology. The use of high-resolution CT and MR scans has shown that the diameter of APA is generally smaller than 20 mm and often smaller than 10 mm (25). In this study 45% of the APAs discovered by CT or MR were smaller than 20 mm, and 17% were smaller than 10 mm. This finding accords well with the 12.4-mm mean diameter of a recent report (42). Because these small tumors can escape detection with all imaging techniques, it is not surprising that they could be accurately identified with CT or MR only in about one-half of the cases (42). Considering the high prevalence of arterial HT (22) and incidentally discovered adrenal masses (43), of which only 1.6% are APAs (44), the concurrence by chance of primary HT and nonfunctioning adrenal tumors is, according to conditional probability calculation (Bayes rule), about 3.6%.

We and others proposed that AVS is crucial to show lateralization of aldosterone secretion from the affected adrenal gland in the commonly occurring small-sized APA (25,42,45). Hence, the lack of performing AVS might affect the proportion of PA attributed to APA or IHA. This hypothesis, which has never been tested in a large multicenter study, was confirmed by comparing the diagnoses made at the centers that could perform AVS with those made at the centers where this test was unavailable: the former centers diagnosed more APAs than the latter centers, where more cases of PA had to be attributed to IHA. Therefore, an accurate diagnosis of the adrenocortical pathology underlying PA requires AVS. This test is technically demanding and not universally available, but can be performed at a very low (0.5% to 1%) risk of major complications in experienced hands (42,46).

Conclusions. Almost 5% of the newly diagnosed hypertensive patients who are referred to specialized centers for HT have a surgically curable APA. However, this figure might underestimate the true prevalence of the tumors because of the lack of systematic use of AVS. An additional 6.4% of case had IHA, thus resulting in an overall prevalence of PA of about 11.2%. Given the high prevalence of

arterial HT, screening for PA is warranted in newly diagnosed hypertensive patients. The biochemical identification of PA represents a compelling indication for the search of a unilateral adrenal cause of aldosterone excess, which is feasible with AVS and is mandatory before undertaking adrenalectomy.

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REFERENCES

1. Conn JW. Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* 1955;45:3–17.
2. Rossi GP. Primary aldosteronism: a needle in a haystack or a yellow cab on Fifth Avenue? *Curr Hypertens Rep* 2004;6:1–4.
3. Gordon RD, Ziesak MD, Tunny TJ, et al. Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin Exp Pharmacol Physiol* 1993;20:296–8.
4. Anderson GH Jr., Blakeman N, Streeten DHM. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens* 1994;12:609–15.
5. Gordon RD, Stowasser M, Tunny TJ, et al. High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol* 1994;21:315–8.
6. Abdelhamid S, Muller LH, Pahl S, et al. Prevalence of adrenal and extra-adrenal Conn syndrome in hypertensive patients. *Arch Intern Med* 1996;156:1190–5.
7. Rossi GP, Rossi E, Pavan E, et al. Screening for primary aldosteronism with a logistic multivariate discriminant analysis. *Clin Endocrinol (Oxf)* 1998;49:713–23.
8. Rayner BL, Opie LH, Davidson JS. The aldosterone/renin ratio as a screening test for primary aldosteronism. *S Afr Med J* 2000;90:394–400.
9. Loh KC, Koay ES, Khaw MC, et al. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab* 2000;85:2854–9.
10. Fardella CE, Mosso L, Gomez-Sanchez C, et al. Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab* 2000;85:1863–7.
11. Lim PO, Dow E, Brennan G, et al. High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens* 2000;14:311–5.
12. Rayner BL, Myers JE, Opie LH, et al. Screening for primary aldosteronism—normal ranges for aldosterone and renin in three South African population groups. *S Afr Med J* 2001;91:594–9.
13. Calhoun DA, Nishizaka MK, Zaman MA, et al. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 2002;40:892–6.
14. Rossi E, Regolisti G, Negro A, et al. High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. *Am J Hypertens* 2002;15:896–902.
15. Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clin Chem* 2005;51:386–94.
16. Omura M, Sasano H, Fujiwara T, et al. Unique cases of unilateral hyperaldosteronemia due to multiple adrenocortical micronodules, which can only be detected by selective adrenal venous sampling. *Metabolism* 2002;51:350–5.
17. Ferris JB, Brown JJ, Fraser R, et al. Hypertension with aldosterone excess and low plasma renin: operative distinction between patients with and without adrenocortical tumour. *Lancet* 1970;2:995–1000.
18. Olivieri O, Ciacciarelli A, Signorelli D, et al. Aldosterone to renin ratio in a primary care setting: the Bussolengo study. *J Clin Endocrinol Metab* 2004;89:4221–6.

19. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6.
20. Rossi GP, Bernini G, Desideri G, et al. Renal damage in primary aldosteronism. *Hypertension* 2006;48:232-8.
21. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD Statement for Reporting Studies of Diagnostic Accuracy: explanation and elaboration. *Clin Chem* 2003;49:7-18.
22. Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.
23. Kem DC, Weinberger MH, Mayes DM, et al. Saline suppression of plasma aldosterone in hypertension. *Arch Intern Med* 1971;128:380-6.
24. Giacchetti G, Ronconi V, Lucarelli G, et al. Analysis of screening and confirmatory tests in the diagnosis of primary aldosteronism: need for a standardized protocol. *J Hypertens* 2006;24:737-45.
25. Rossi GP, Sacchetto A, Chiesura-Corona M, et al. Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. *J Clin Endocrinol Metab* 2001;86:1083-90.
26. Rossi GP, Chiesura-Corona M, Gregianin M. Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* 1995;123:73-4.
27. Rossi GP, Ganzaroli C, Miotto D, et al. Dynamic testing with high-dose adrenocorticotropic hormone does not improve lateralization of aldosterone oversecretion in primary aldosteronism patients. *J Hypertens* 2006;24:371-9.
28. Abdelhamid S, Blomer R, Hommel G, et al. Urinary tetrahydroaldosterone as a screening method for primary aldosteronism: a comparative study. *Am J Hypertens* 2003;16:522-30.
29. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Available at: <http://www.kdoqi.org>. Accessed July 8, 2006.
30. Rundback JH, Sacks D, Kent KC, et al. Guidelines for the reporting of renal artery revascularization in clinical trials. American Heart Association. *Circulation* 2002;106:1572-85.
31. 1999 World Health Organization. International Society of Hypertension guidelines for the management of hypertension. Guidelines Subcommittee. *J Hypertens* 1999;17:151-83.
32. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839-43.
33. Fiad TM, Cunningham SK, Hayes FJ, et al. Effects of nifedipine treatment on the renin-angiotensin-aldosterone axis. *J Clin Endocrinol Metab* 1997;82:457-60.
34. Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension* 2002;40:897-902.
35. Tiu SC, Choi CH, Shek CC, et al. The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling. *J Clin Endocrinol Metab* 2005;90:72-8.
36. Rossi G, Boscaro M, Ronconi V, et al. Aldosterone as a cardiovascular risk factor. *Trends Endocrinol Metab* 2005;16:104-7.
37. Rossi GP, Sacchetto A, Pavan E, et al. Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma. *Circulation* 1997;95:1471-8.
38. Brown MA, Cramp HA, Zammit VC, et al. Primary hyperaldosteronism: a missed diagnosis in 'essential hypertensives'? *Aust N Z J Med* 1996;26:533-8.
39. Kaplan NM. The current epidemic of primary aldosteronism: causes and consequences. *J Hypertens* 2004;22:863-9.
40. Mulatero P, Dluhy RG, Giacchetti G, et al. Diagnosis of primary aldosteronism: from screening to subtype differentiation. *Trends Endocrinol Metab* 2005;16:114-9.
41. Mulatero P, Stowasser M, Loh KC, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab* 2004;89:1045-50.
42. Young WF, Stanson AW, Thompson GB, et al. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004;136:1227-35.
43. Kloos RT, Gross MD, Francis IR, et al. Incidentally discovered adrenal masses. *Endocr Rev* 1995;16:460-84.
44. Mantero F, Masini AM, Opocher G, et al. Adrenal incidentaloma: an overview of hormonal data from the National Italian Study Group. *Horm Res* 1997;47:284-9.
45. Magill SB, Raff H, Shaker JL, et al. Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. *J Clin Endocrinol Metab* 2001;86:1066-71.
46. Daunt N. Adrenal vein sampling: how to make it quick, easy, and successful. *Radiographics* 2005;25 Suppl 1:S143-58.

APPENDIX

For a list of author affiliations and supplemental table, please see the online version of this article.