Hypertension

ORIGINAL ARTICLE

Long-Term Follow-Up of Patients With Elevated Aldosterone-to-Renin Ratio but Negative Confirmatory Test: The Progression of Primary Aldosteronism Phenotypes

Fabrizio Buffolo,* Alessio Pecori,* Martin Reincke,* Merve Outland, Franco Veglio, Paul Schwarzlmüller, Martin Bidlingmaier, Sonja Kunz, Christopher Stremmel, Giulio Mengozzi, Gabriella Priolo, Paolo Mulatero, Christian Adolf,† Silvia Monticone†

BACKGROUND: About 10% of patients with arterial hypertension have a positive screening test for primary aldosteronism (PA) and 50% to 70% of them have a negative confirmatory test: the appropriate follow-up of these patients is currently unknown. We investigated the incidence of PA in patients with previous negative confirmatory testing, after at least a 2-year follow-up.

METHODS: One hundred eighty-four patients with a previously elevated aldosterone-to-renin ratio followed by a negative confirmatory test were recruited in 2 hypertension centers (Torino and Munich). We repeated the screening test for PA and, if positive, the confirmatory test (seated saline infusion test or captopril challenge test). Primary end point of the study was the incidence of newly diagnosed overt PA, as defined by a positive confirmatory test.

RESULTS: After a mean follow-up of 5 years, 20% of patients developed overt PA. When subtype diagnosis was offered systematically, one-third of patients displayed unilateral PA. Patients who developed PA showed worsening of blood pressure control and a higher rate of cardiac organ damage, despite similar implementation of antihypertensive therapy, compared with patients without PA. A mild progression of autonomous aldosterone secretion was evident even in patients without confirmed PA but with relatively stable control of blood pressure levels over time.

CONCLUSIONS: About one-fifth of patients with a negative confirmatory test develop overt PA over time. A clinical follow-up of patients with a negative confirmatory test is advisable, along with the repetition of PA investigation, primarily in patients with worsening of blood pressure control. ***(Hypertension.* 2024;81:340–347. DOI: 10.1161/HYPERTENSIONAHA.123.21983.)** • **Supplement Material**.

Key Words: adenoma ■ aldosterone ■ blood pressure ■ hypertension ■ renin

In the last decade, several publications developed and validated the concept of renin independent aldosterone production,[1–3] ranging from the mildest forms of autonomous but still suppressible aldosteronism to biochemically overt primary aldosteronism (PA), across the whole spectrum of blood pressure levels.[4]

About one-third of patients with hypertension have a low renin phenotype,[5] and 9% to 14% of the general

Correspondence to: Paolo Mulatero, Division of Internal Medicine 4 and Hypertension Unit, Department of Medical Sciences, University of Torino, Città della Salute e della Scienza di Torino, Via Genova 3, 10126 Torino, Italy. Email paolo.mulatero@unito.it
*F. Buffolo, A. Pecori, and M. Reincke contributed equally as joint first authors.
†C. Adolf and S. Monticone contributed equally as joint last authors.
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NOVELTY AND RELEVANCE

What Is New?

One-fifth of patients with previous negative confirmatory test for primary aldosteronism (PA) develop overt PA over time and, when subtype diagnosis is investigated, one-third of them have a unilateral and thus surgically curable form.

What Is Relevant?

A repetition of the diagnostic workup should be offered to patients with a negative confirmatory test for PA, especially to those who show scarce control of blood pressure at follow-up.

Clinical/Pathophysiological Implications?

PA is not a dichotomous and definitive disease but a continuous condition that ranges and evolves from mild autonomous aldosterone secretion toward the classical overt form of PA.

Nonstandard Abbreviations and Acronyms

APM	aldosterone-producing micronodule
AVS	adrenal venous sampling
PA	primary aldosteronism
PRA	plasma renin activity
ROARR	Repetition of Aldosterone-to-Renin Ratio
SSIT	seated saline infusion test

hypertensive population have a positive screening test for PA.[6,7] Biochemically overt PA, characterized by autonomous aldosterone secretion, not suppressible by traditional confirmatory tests, is present in about 6% of patients with arterial hypertension[6] and in ≈30% of patients with resistant hypertension[8] or hypertension and hypokalemia.[9] Overt PA is associated with cardiovascular damage,[10] renal damage,[11] increased risk of cardiovascular events,[12] and death.[13] Nevertheless, the risk of cardiac damage and cardiovascular events is not exclusive for overt PA but seems to progress across the continuum of PA phenotypes.[14,15]

Aldosterone-producing micronodules (APMs) are small clusters of aldosterone synthase (CYP11B2) expressing cells, which can harbor similar aldosterone-stimulating somatic driver mutations than aldosterone-producing adenomas,[16] and have been implicated in the age-related increase of autonomous aldosterone secretion.[3] Some authors hypothesized that APM accumulation could represent the histopathologic basis of bilateral PA[17] and aldosterone-producing adenomas might arise from APM.[16]

Although the reported results suggest that low renin hypertension can evolve in overt PA during time, no definitive evidence is currently available to support this hypothesis. We, therefore, designed the ROARR study (Repetition of Aldosterone-to-Renin Ratio), to prospectively investigate the incidence of PA in a cohort of patients with a previous positive screening test, but negative confirmatory test.

METHODS

Data Availability

The complete data set that supports the findings of this study is available from the corresponding author upon reasonable request.

Patient Selection

The protocol was approved by the local ethical committees of the participant centers. Written informed consent was obtained from all the patients recruited in the study.

We prospectively enrolled patients with arterial hypertension with previous positive screening test and negative confirmatory test for PA in 2 different centers: the Division of Internal Medicine 4, Hypertension Unit of the University of Torino, and the Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians University of München.

We included patients aged <65 years at the time of initial confirmatory test and a minimum of 2-year follow-up and a maximum 8-year follow-up time. We excluded patients with other secondary forms of arterial hypertension, normotension at follow-up, and patients unwilling to repeat screening and confirmatory test for PA.

PA Diagnosis

We established the diagnosis of PA according to the recommendations of the Endocrine Society and European Society of Hypertension.[18–20] We withdrew interfering drugs before biochemical screening. When the complete withdrawal of antihypertensive drugs was unfeasible, the screening test was performed with medications that have none or only a minimal influence on the aldosterone-to-renin ratio (α1-antagonists, dihydropyridine and nondihydropyridine calcium channel blockers, moxonidine). We calculated the daily defined dose of antihypertensive drugs to estimate the intensity of antihypertensive therapy, before treatment modifications.

We interpreted the screening and confirmatory test results according to the local criteria of each recruiting center. In Torino,

the screening tests were considered positive with aldosterone-to-renin ratio ≥30 ng dL^{-1} ng^{-1} mL^{-1} h^{-1} and aldosterone ≥10 ng dL^{-1}. In Munich, the screening tests were considered positive with aldosterone-to-renin ratio ≥1.2 ng dL^{-1} mU^{-1} L^{-1} and aldosterone ≥6 ng dL^{-1}. Confirmation of PA was performed through seated saline infusion test (SSIT) or captopril challenge test (in case of contraindications for saline load) and interpreted with the local criteria specific for each center. In Torino, PA was confirmed with aldosterone post-SSIT ≥6 ng dL^{-1}, or ARR ≥30 ng dL^{-1} ng^{-1} mL^{-1} h^{-1} after captopril challenge test. In Munich, PA was confirmed with aldosterone post-SSIT ≥6 ng dL^{-1} or <30% decline of aldosterone levels after captopril challenge test. Interpretation criteria for screening and confirmatory tests were the same at the first evaluation and at follow-up, within each center. Methods for renin/plasma renin activity (PRA) and aldosterone measurements were the same at the first evaluation and at follow-up, within each center. In Torino, aldosterone concentrations and PRA were measured by radioimmunoassay. In Munich, aldosterone and renin concentration were measured by chemiluminescent immunoassay.

Subtype diagnosis was obtained by adrenal computed tomography and adrenal venous sampling (AVS), according to ES and European Society of Hypertension recommendations.[18,20] In Torino, AVS was offered to all patients with confirmed PA. In Munich, AVS was offered to patients with confirmed PA and at least moderate probability of unilateral PA, defined with SPACE (Subtyping Primary Aldosteronism by Clinical Evaluation) score >8.[21]

We calculated the Score To Predict Primary Aldosteronism and random forest regressor model for PA prediction at the first visit and follow-up, as previously described.[22]

Hypertension-Mediated Organ Damage

Cardiac hypertension-mediated organ damage was defined as concentric remodeling or left ventricular hypertrophy according to the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[23,24] Albuminuria was considered significant when ≥30 mg 24 h^{-1}.[24]

End Points of the Study

Primary end point of the study was the incidence of newly diagnosed PA, according to the criteria defined above. Secondary exploratory end points included the percentage of unilateral PA in patients with newly diagnosed PA, changes in aldosterone levels, renin/PRA, blood pressure levels, and intensity of antihypertensive treatment at follow-up.

Statistical Analysis

Variables were treated as parametric or nonparametric according to their distribution. Continuous variables with a normal distribution were reported as mean±SD. Non-normally distributed data were reported as median (interquartile range). Categorical data were expressed as absolute number and percentage. For normally distributed data, statistical significance was calculated by the Student *t* test for independent samples and paired *t* test for dependent samples. For non-normally distributed data, the Mann-Whitney *U* test was applied for independent variables and Wilcoxon signed-rank test for paired variables. χ^2 was used for comparison of categorical variables. Multivariate linear regression was adopted to predict aldosterone post-SSIT at follow-up.

RESULTS

Characteristics of Cohorts

In the ROARR study, we prospectively enrolled 184 patients: 101 in Torino and 83 in Munich. At the first visit, the cohorts were similar in terms of age, hypertension severity, antihypertensive treatments, and potassium levels (Table 1). The cohort from Munich had a greater proportion of women and lower aldosterone levels than patients from Torino. Follow-up times were similar in the 2 centers: 4.9±2.3 years in Torino and 4.8±2.3 years in Munich (*P*=0.625). At the follow-up visit, in the entire

Table 1. Characteristics of Patients

Visit	First visit			Second visit		
Variables	Torino (n=101)	Munich (n=83)	*P* value	Torino (n=101)	Munich (n=83)	*P* value
Female sex, n (%)	50 (49.5)	63 (75.9)	<0.001*	…	…	…
Age, y	48±8	46±11	0.064	53±9	50±10	0.055
Follow-up, y	…	…	…	4.9±2.3	4.8±1.5	0.625
SBP, mm Hg	147±15	145±16	0.524	133±14	138±13	0.011*
DBP, mm Hg	93±10	93±11	0.823	84±8	89±9	<0.001*
DDD	1.00 (0.50–3.00)	1.00 (0.00–2.50)	0.140	2.00 (1.15–3.58)	2.00 (0.50–3.00)	0.295
Potassium, mmol L^{-1}	4.1±0.4	4.1±0.4	0.861	3.9±0.4	4.3±0.3	<0.001*
Creatinine, mg dL^{-1}	0.84±0.21	0.84±0.19	0.963	0.85±0.19	0.86±0.18	0.651
Screening test PRA, ng mL^{-1} h^{-1}	0.30 (0.19–0.45)	…	…	0.48 (0.25–1.21)	…	…
Screening test renin, μU mL^{-1}	…	3.5 (2.0–5.6)	…	…	6.3 (2.8–11.0)	…
Screening test aldosterone, ng dL^{-1}	20.5 (16.3–27.7)	9.3 (7.8–13.4)	<0.001*	18.9 (8.1–24.8)	11.2 (8.5–14.6)	<0.001*

The comparison of clinical and biochemical characteristics of patients recruited in Torino (n=101) and in Munich (n=83). The first visit was performed before the current study while the second visit was part of the present study. Variables are reported as mean±SD, median (interquartile range), or absolute number (percentage, %), as appropriated. DDD: average maintenance dose per day for a drug used for its main indication in adults. DBP indicates diastolic blood pressure; DDD, defined daily dose; PRA, plasma renin activity; and SBP, systolic blood pressure.

*Differences were considered significant when *P*<0.05.

cohort, patients showed increased intensity of antihypertensive therapy (daily defined dose, 2.00 [1.00–3.25] versus 1.00 [0.25–3.00]; $P<0.001$), with consequent reduction of blood pressure levels (135±14 versus 146±16 mm Hg for systolic blood pressure, $P<0.001$; 86±9 versus 93±10 mm Hg for diastolic blood pressure, $P<0.001$).

Incidence and Characteristics of Patients With PA at Follow-Up

Ninety-five of 184 patients (52%) had a positive screening test at follow-up and 36 (20% of the entire cohort) had PA diagnosis confirmed by SSIT or captopril challenge test (Figure 1). The incidence of positive screening test and PA diagnosis was similar in the 2 centers ($P=0.127$ and $P=0.160$, respectively). Among the 89 patients with negative screening test, 42 patients had PRA or renin no longer suppressed (considering a threshold of PRA ≥1.00 ng mL^{-1} h^{-1} and renin ≥15 μU mL^{-1}).

In Munich, 14 of 20 patients with confirmed PA had low probability of unilateral PA (SPACE score, <8)[21] and subtype diagnosis was not investigated. AVS was offered to the remaining 6 patients: 5 patients refused AVS and 1 AVS procedure was unsuccessful. In Torino, AVS was offered systematically to all patients with confirmed PA: 5 (31%) had unilateral PA, 7 (44%) had bilateral PA, and 4 (25%) patients either refused AVS or AVS was unsuccessful (Figure 1A through 1C). Two of 5 patients with unilateral PA underwent unilateral adrenalectomy, while 3 patients refused surgical intervention. According to the Primary Aldosteronism Surgery Outcome criteria,[25] following adrenalectomy, we observed a complete clinical outcome in 1 patient and partial clinical outcome in the other. Biochemical outcome was complete (cure of PA) in both the patients.

In next step, we analyzed the initial phenotypes at the first presentation of our cohort stratified according to later confirmed PA diagnosis. At the first visit, patients with confirmed PA at follow-up did not differ in clinical and biochemical characteristics (including hormonal parameters at the first screening test) from patients without PA (Table 2). The Score To Predict Primary Aldosteronism and random forest regressor coefficients, calculated as previously described,[22] were similar in patients with and without PA (Table 2). However, patients with PA had slightly higher aldosterone concentration post-SSIT at the first visit, than patients without PA (Table 2).

At the second screening test, patients with PA had lower renin/PRA and higher aldosterone levels than patients without PA (Table 2). The intensity of antihypertensive treatment was similar in patients with PA and non-PA, but patients with PA had higher blood pressure levels than patients without PA. The Score To Predict Primary Aldosteronism and random forest regressor coefficients were significantly higher in patients with PA, compared with patients without PA at the second visit (Table 2). Among patients with available transthoracic echocardiography at the second visit (n=104), patients with PA displayed higher rate of cardiac hypertension-mediated

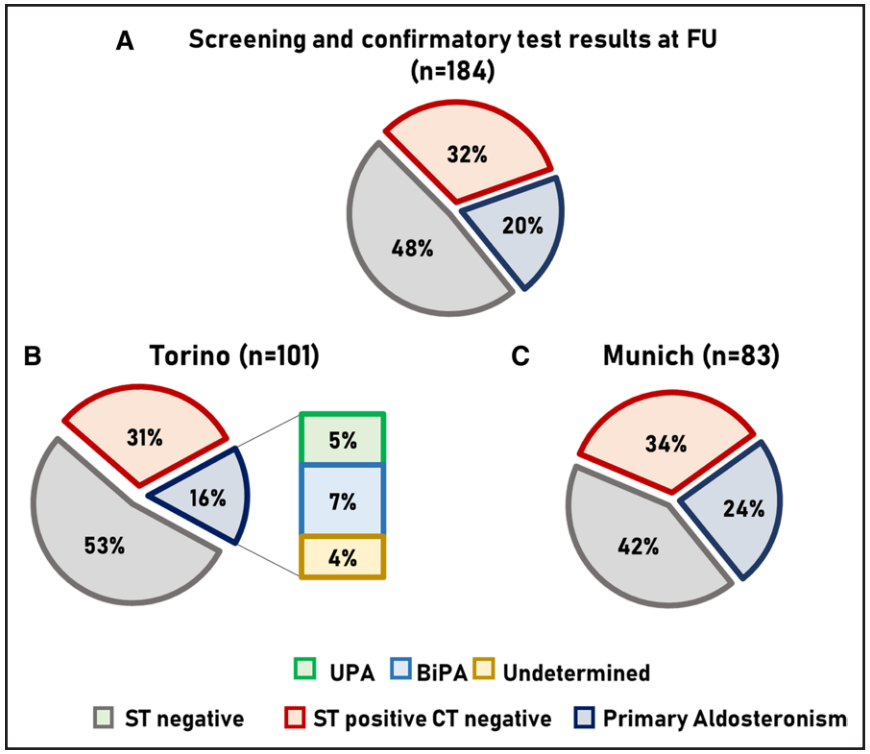

Figure 1. Incidence of primary aldosteronism (PA).
The pie charts show the results of the screening test (ST) and confirmatory test (CT) at follow-up (FU) in patients who had previous positive screening test and negative confirmatory test at the first visit. A, In the entire cohort. B, In Torino. C, In Munich. In Torino (B), patients with PA were further divided according to subtype diagnosis: unilateral PA (UPA), bilateral PA (BiPA), and undetermined.

Table 2. Comparison of Patients With PA Diagnosis at Follow-Up and Patients Without PA

Visit	First visit			Second visit		
Variables	Non-PA (n=148)	PA (n=36)	*P* value	Non-PA (n=148)	PA (n=36)	*P* value
Female sex, n (%)	90 (60.8%)	23 (63.9%)	0.734	…	…	…
Age, y	47±10	46±8	0.645	52±10	51±8	0.483
SBP, mm Hg	146±15	147±18	0.343	133±12	142±17	0.005*
DBP, mm Hg	93±11	94±10	0.243	85±9	89±8	0.007*
DDD	1.00 (0.00–2.50)	1.58 (0.81–3.00)	0.122	2.00 (1.00–3.46)	2.13 (0.81–3.00)	0.941
Potassium, mmol L^{-1}	4.1±0.4	4.0±0.3	0.373	4.1±0.4	4.0±0.4	0.195
Creatinine, mg dL^{-1}	0.84±0.21	0.82±0.16	0.538	0.86±0.19	0.85±0.15	0.385
Screening test PRA, ng mL^{-1} h^{-1}†	0.30 (0.20–0.42)	0.25 (0.12–0.49)	0.405	0.72 (0.25–1.51)	0.30 (0.24–0.46)	0.023*
Screening test renin, μU mL^{-1}‡	3.7 (2.0–6.1)	3.2 (2.0–5.1)	0.422	7.0 (3.0–12.9)	4.8 (2.1–7.4)	0.013*
Screening test aldosterone, ng dL^{-1}	16.5 (9.4–24.4)	12.9 (8.4–26.6)	0.366	13.9 (6.7–19.7)	17.8 (12.6–26.7)	<0.001*
Aldosterone post-SSIT, ng dL^{-1}§	3.3 (2.5–4.6)	3.9 (3.1–5.0)	0.035*	4.6 (3.5–5.5)	8.1 (7.0–10.1)	<0.001*
SToP-PA score	8.5 (6.0–10.5)	9.5 (6.5–11.0)	0.229	8.5 (6.0–10.5)	10.0 (7.0–11.5)	0.046*
RFr coefficient	0.26 (0.00–0.45)	0.32 (0.25–0.44)	0.183	0.30 (0.25–0.44)	0.35 (0.26–0.56)	0.019*

The comparison of clinical and biochemical characteristics of patients without PA (n=148) and with confirmed PA (n=36). The first visit was performed before the present study while the second visit was part of the present study. Variables are reported as mean±SD, median (interquartile range), or absolute number (%), as appropriated. DDD: average maintenance dose per day for a drug used for its main indication in adults. DBP indicates diastolic blood pressure; DDD, defined daily dose; PA, primary aldosteronism; PRA, plasma renin activity; RFr, random forest regressor; SBP, systolic blood pressure; SSIT, seated saline infusion test; and SToP-PA, Score To Predict Primary Aldosteronism.

*Differences were considered significant when $P<0.05$.

†PRA was measured and compared in patients from Torino.

‡Renin was measured and compared in patients from Munich.

§The comparison was performed in the subgroups of patients who performed SSIT at the first visit and at the second visit.

organ damage[23] than patients without PA (14/23 [60.9%] versus 29/81 [35.8%]; $P=0.031$). In patients with and without PA, the 24-hour albuminuria (10.8 [8.4–13.2] versus 8.8 [6.6–14.0] mg per 24 hours; $P=0.180$] and the rate of patients with albuminuria >30 mg per 24 hours (13/112 [11.6%] versus 2/31 [6.5%]; $P=0.407$) were similar.

We then compared patients with normal renin at the second screening (PRA, ≥1.00 ng mL^{-1} h^{-1} and renin, ≥15 μU mL^{-1}) versus patients with persistent low renin (Table S1). We identified a nonsignificant trend toward a high systolic blood pressure at the second visit in patients with persistent low renin (134±12 versus 131±12 mm Hg, $P=0.075$), despite similar intensity of antihypertensive treatment ($P=0.398$). Among patients with available echocardiography at the second visit, the prevalence of cardiac hypertension-mediated organ damage was similar in the 2 groups (6/18 [33.3%] versus 23/63 [36.5%]; $P=0.804$).

Progression of Autonomous Aldosterone Secretion

Considering patients who performed SSIT at the first visit and follow-up, aldosterone post-SSIT increased significantly in the entire cohort (3.5 [2.9–4.7] versus 5.6 [4.0–7.5] ng dL^{-1}; $P=0.002$), in the PA group (4.1 [3.1–4.9] versus 8.0 [6.9–12.8] ng dL^{-1}; $P<0.001$) and non-PA group (3.3 [2.3–4.3] versus 4.5 [3.5–5.4] ng dL^{-1}; $P<0.001$; Figure 2A through 2C). We then performed a multivariate linear regression to predict aldosterone post-SSIT at follow-up, using age at the first visit, follow-up interval, and aldosterone post-SSIT at the first visit as covariates. There were no significant associations in patients with PA (Table S2). However, among patients without PA, aldosterone post-SSIT at follow-up was significantly and positively associated with aldosterone post-SSIT at the first visit (β, 0.781 [0.499–1.062]; $P<0.001$) and follow-up time (β, 0.262 [0.005–0.520]; $P=0.046$; Table S3 ; Figure 2D).

DISCUSSION

Over the last 2 decades, several international guidelines have been developed, making the diagnostic workup for PA a straightforward 3-step process. A positive screening test should be followed by at least 1 suppression test to confirm or exclude PA diagnosis, unless the patients display a florid phenotype with aldosterone >20 ng dL^{-1}, undetectable renin levels, and hypokalemia.[18,19] In patients with confirmed PA, adrenal computed tomography and adrenal vein sampling are recommended to distinguish between unilateral and bilateral disease and to address patients to surgery.[18,20] However, the natural history of patients with a negative confirmatory test and hence the need for a specific follow-up are currently unknown.

In the prospective ROARR study, we investigated, for the first time, the incidence of PA in a large cohort of 184 patients with a previous positive screening test, followed

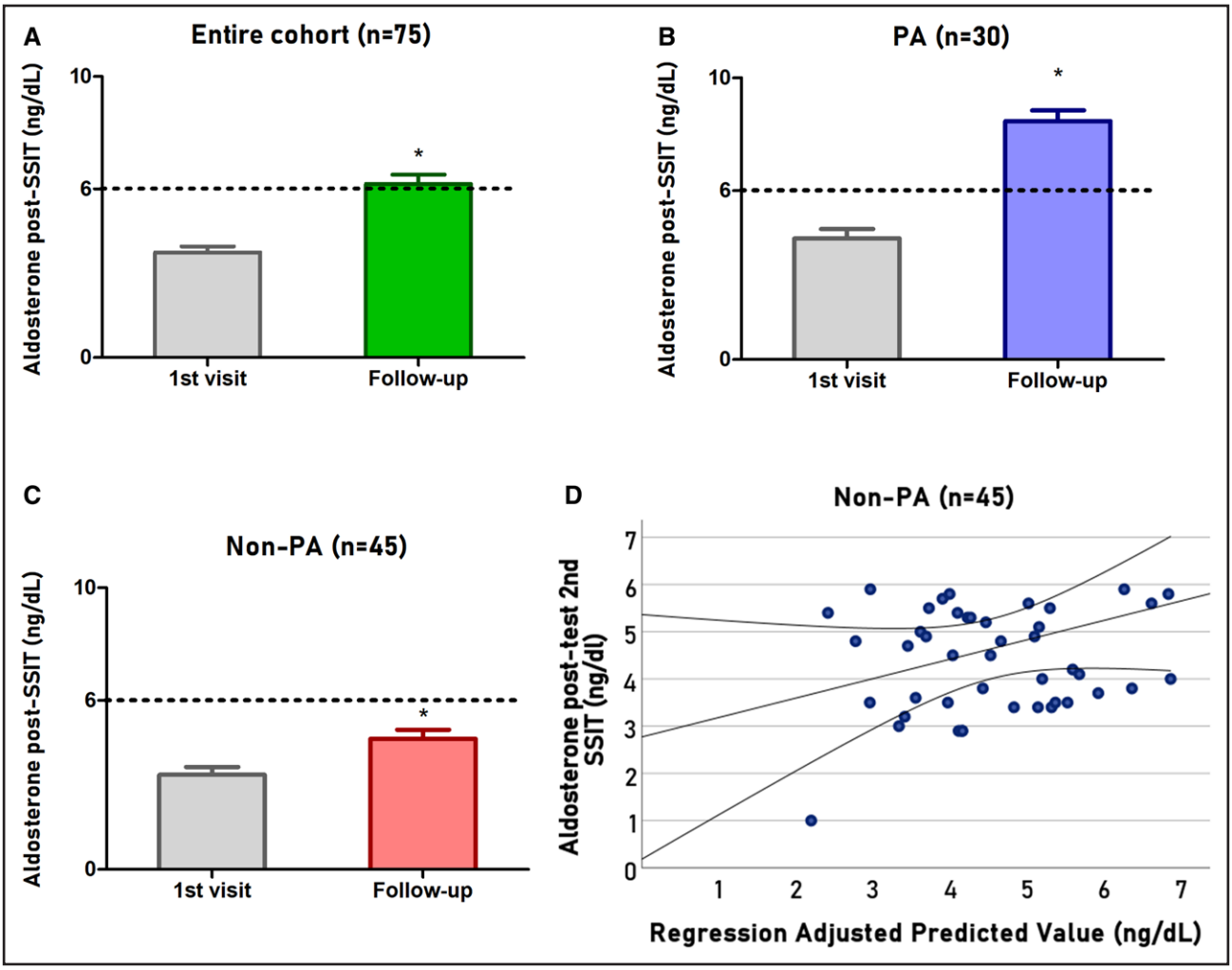

Figure 2. Progression of aldosterone suppressibility.
The charts show the comparison of aldosterone post-seated saline infusion test (SSIT) at the first visit and follow-up of patients who performed SSIT at both visits. **A**, In the entire cohort. **B**, In patients with primary aldosteronism (PA). **C**, In patients without PA at follow-up. The scatterplot (**D**) shows the correlation between aldosterone post-SSIT at follow-up and the adjusted predicted values of the linear regression showed in Table S3. Differences were considered significant when *P<0.05.

by a negative confirmatory test. After a mean follow-up time of 5 years, one-fifth of the included patients progressed from low renin essential hypertension to overt PA and, after subtype investigation, one-third of these patients showed a surgically amenable unilateral form.

We also looked at the predictors associated with the development of PA, to identify those patients who might benefit for further follow-up hormonal testing. While at the first visit patients who developed PA at follow-up had only modestly higher aldosterone values post-SSIT, at follow-up visit, they had significantly higher blood pressure levels, despite similar intensity of antihypertensive treatment. In particular, patients who developed PA had mean systolic blood pressure values above the threshold of grade 1 hypertension.[24] All patients with unilateral PA had systolic blood pressure above the targets of the European Society of Hypertension, and 4 out of 5 patients displayed a remarkable increase in blood pressure at follow-up, with grade 2 hypertension despite antihypertensive treatment. The relevance of this finding is underlined by a higher incidence of hypertension-mediated organ damage in patients who developed PA. In agreement with these observations, the Score To Predict Primary Aldosteronism and random forest regressor coefficients[22] became significantly different at the second visit in patients with and without PA at follow-up.

On the basis of these findings, it could be reasonable to suggest a clinical follow-up of all patients with a negative confirmatory test and to repeat the screening test in those who display a progressive increase in blood pressure levels or scarce control of blood pressure, despite an adequate implementation of antihypertensive therapy.

It should be noted that, in 23% of the patients, renin levels were no longer suppressed at follow-up and about

half of the patients had a negative screening test at the second visit. This is not surprising, considering the renin variability that is observed in patients without PA,[26] justified by several factors, in particular dietary sodium intake.[27,28] However, at least in our study, dietary sodium intake estimated by 24-hour urinary sodium excretion was unaltered at follow-up.

The historical dichotomic difference between essential hypertension and PA has been challenged by preclinical and clinical studies showing that PA is a continuum that ranges from the mildest form of renin-independent aldosteronism toward the biochemically and clinically overt PA.[4] A large cross-sectional study[3] showed that older age is associated with progressive inability to physiologically modulate aldosterone production, in patients without PA. Our findings corroborate these observations through longitudinal follow-up of patients with autonomous but still suppressible aldosteronism. We showed that, in patients without confirmed PA, the suppressibility of aldosterone secretion is progressively reduced over time, although beneath the thresholds that define overt PA. In these patients, the hypertensive phenotype remains relatively stable in terms of blood pressure control and potassium levels. On the contrary, in patients with confirmed PA, aldosterone becomes overtly unsuppressible, independently from the follow-up interval between the first and second visits. In these patients, the biochemical evolution of PA parallels the worsening of the clinical phenotype, particularly in patients with unilateral forms. The discoveries of APMs, in adrenal glands of patients with and without PA, expanded our knowledge of the histopathologic basis of renin independent aldosterone production[3,16] and could explain the progression of PA phenotypes that we reported in our study. In patients without PA, APMs numbers and total area increase with age,[3] and this could represent the basis of age-related renin-independent aldosterone secretion that we prospectively observed in our cohorts, in agreement with previous studies.[3]

The strengths of our study are the prospective design, the long-term follow-up and the similar results reported in the 2 different centers. A limit of the study is that the screening test at the first visit was performed only once before the confirmatory test.

CONCLUSIONS

In the ROARR study we report, for the first time, the natural history of patients with positive screening test for PA and negative confirmatory test showing that 20% of these patients develop overt PA. These data should encourage the clinicians to repeat a PA screening test and, whether positive, a suppression test in patients with previous negative confirmatory test, especially in those with scarce control of blood pressure levels during follow-up, which have high probability of PA and unilateral PA. Patients with newly diagnosed PA should probably undergo a complete subtype diagnosis, considering that in our cohort one-third of patients have a unilateral form that may benefit of surgical cure.

ARTICLE INFORMATION

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Affiliations

Division of Internal Medicine 4 and Hypertension Unit, Department of Medical Sciences (F.B., A.P., F.V., P.M., S.M.), Department of Laboratory Medicine (G.M., G.P.), University of Torino, Italy. Medizinische Klinik und Poliklinik IV, Department of Medicine IV (M.R., M.O., P.S., M.B., S.K., C.A.), Medizinische Klinik und Poliklinik I (C.S.), Klinikum der Universität, Ludwig-Maximilians-Universität München, Munich, Germany.

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