The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 11, e4340–e4349
https://doi.org/10.1210/clinem/dgab482
Clinical Research Article

Clinical Research Article

Identification of Surgically Curable Primary Aldosteronism by Imaging in a Large, Multiethnic International Study

Gian Paolo Rossi,[1] Filippo Crimì,[2] Giacomo Rossitto,[1] Laurence Amar,[3,4] Michel Azizi,[3,4] Anna Riester,[5] Martin Reincke,[5] Christoph Degenhart,[5] Jiri Widimsky,[6] Mitsuhide Naruse,[7] Jaap Deinum,[8] Leo Schultze Kool,[9] Tomaz Kocjan,[10,11] Aurelio Negro,[12] Ermanno Rossi,[12] Gregory Kline,[13] Akiyo Tanabe,[14] Fumitoshi Satoh,[15] Lars Christian Rump,[16] Oliver Vonend,[16] Holger S. Willenberg,[17] Peter J. Fuller,[18,19] Jun Yang,[18,19,20] Nicholas Yong Nian Chee,[18] Steven B. Magill,[21] Zulfiya Shafigullina,[22] Marcus Quinkler,[23] Anna Oliveras,[24] Vin Cent Wu,[25] Zuzana Kratka,[6] Giulio Barbiero,[2] Teresa Maria Seccia,[1] and Michele Battistel[2]

[1]University of Padova, Department of Medicine-DIMED, International PhD Program in Arterial Hypertension and Vascular Biology (ARHYVAB), University Hospital, 35128 Padova, Italy; [2]University of Padova, Department of Medicine-DIMED, Institute of Radiology, University Hospital, 35128 Padova, Italy; [3]AP-HP, Hôpital Européen Georges-Pompidou, Hypertension Department and DMU CARTE, F-75015 Paris, France; [4]Université de Paris, INSERM, CIC1418 and UMR 970, F-75015 Paris, France; [5]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, 80336 Munich, Germany; [6]3rd Department of Medicine, Charles University, General Faculty Hospital, 100 00 Prague, Czech Republic; [7]Department of Endocrinology, Clinical Research Institute, NHO Kyoto Medical Center and Endocrine Center, Ijinkai Takeda General Hospital, 612-8429 Kyoto, Japan; [8]Department of Internal Medicine, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands; [9]Department of Radiology, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands; [10]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center Ljubljana, 1525 Ljubljana, Slovenia; [11]Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia; [12]Department of Internal Medicine, Azienda Unità Sanitaria Locale, IRCCS Arcispedale S. Maria Nuova, Hypertension Unit, 42123 Reggio Emilia, Italy; [13]Foothills Medical Center, University of Calgary, Calgary, Alberta T2N 2T9, Canada; [14]Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, 62-8655 Tokyo, Japan; [15]Division of Nephrology, Endocrinology, and Vascular Medicine, Tohoku University Hospital, 980-8576 Sendai, Japan; [16]Heinrich Heine University Düsseldorf, Nephrologie, 40225 Düsseldorf, Germany; [17]Division of Endocrinology and Metabolism, Rostock University Medical Center, D-18057 Rostock, Germany; [18]Endocrinology Unit, Monash Health, Clayton, Victoria, 3168, Australia; [19]Centre for Endocrinology and Metabolism, Hudson Institute of Medical Research, Clayton, Victoria, 3168, Australia; [20]Department of Medicine, Monash University, Clayton, 3168, Victoria, Australia; [21]Medical College of Wisconsin, Endocrinology Center, North Hills Health Center, Menomonee Falls, Wisconsin 53051, USA; [22]Department of Endocrinology, North-Western Medical University named after I. I. Mechnikov, 191015 Saint Petersburg, Russia; [23]Endocrinology in Charlottenburg, 10627 Berlin, Germany; [24]Department of Nephrology,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Hypertension Unit, Hospital del Mar; Universitat Pompeu Fabra; IMIM (Hospital del Mar Medical Research Institute), 08003 Barcelona, Spain; and [25]Department of Internal Medicine, National Taiwan University Hospital, 100229 Taipei, Taiwan

ORCiD numbers: 0000-0002-7963-0931 (G. P. Rossi); 0000-0001-9023-0835 (G. Rossitto); 0000-0003-3942-4276 (L. Amar); 0000-0003-3231-7435 (A. Riester); 0000-0002-9817-9875 (M. Reincke); 0000-0001-8242-9705 (J. Widimsky); 0000-0002-8977-4090 (M. Naruse); 0000-0003-2465-1986 (J. Deinum); 0000-0001-8606-6825 (T. Kocjan); 0000-0002-5682-4952 (A. Tanabe); 0000-0003-4620-4976 (J. Yang); 0000-0002-9598-4908 (N. Y. N. Chee); 0000-0001-7935-0991 (V. Cent Wu).

Abbreviations: AUC, area under the curve; AVIS-2, Adrenal Vein Sampling International Study 2; AVS, adrenal vein sampling; BP, blood pressure; CT, computed tomography; MR, magnetic resonance; PA, primary aldosteronism; PASO, Primary Aldosteronism Surgery Outcome; ROC, receiver operating characteristic.

Received: 6 April 2021; Editorial Decision: 28 June 2021; First Published Online: 2 July 2021; Corrected and Typeset: 2 August 2021.

Abstract

Context: Adrenal gland imaging is recommended by the current guidelines for the workup of primary aldosteronism (PA). However, its diagnostic performance has not been established in large, multiethnic cohorts of patients who undergo adrenal vein sampling (AVS) and adrenalectomy.

Objective: This work aims to assess the diagnostic accuracy of cross-sectional adrenal imaging.

Methods: This international multicenter study took place in tertiary referral centers. A total of 1625 PA patients seeking surgical cure were enrolled in an international study involving 19 centers in North America, Europe, Asia, and Australia. Of these, 1311 (81%) had imaging data available and 369 (23%), who received a final diagnosis of surgically cured unilateral PA, were examined. Patients underwent AVS and imaging by computed tomography and/or magnetic resonance imaging. The accuracy of detection of unilateral PA at imaging was estimated by the area under the receiver operator characteristics curve using cure (biochemical and/or full clinical success) as the reference at follow-up after unilateral adrenalectomy.

Results: In the cohort of 1311 patients with imaging data available, 34% and 7% of cases showed no detectable or bilateral nodules, respectively. Imaging did not detect the culprit adrenal in 28% of the surgically cured unilateral PA patients. Moreover, the clinical outcome did not differ significantly between the imaging-positive and imaging-negative patients.

Conclusion: Cross-sectional imaging did not identify a lateralized cause of disease in around 40% of PA patients and failed to identify the culprit adrenal in more than one-fourth of patients with unilateral PA.

Key Words: aldosterone, endocrine hypertension, primary aldosteronism, diagnosis, CT, MRI

Primary aldosteronism (PA) is the most common surgically curable form of secondary (curable) arterial hypertension (1-3), but because the referral of PA patients for adrenalectomy requires prior demonstration of a unilateral cause of the disease, only a tiny proportion of eligible patients are surgically treated and ultimately cured. Adrenal vein sampling (AVS), the key test recommended by available guidelines to identify unilateral PA (4-7), being technically challenging, difficult to interpret, and thus available in only a few centers (8), represents the major hurdle in the subtyping of PA patients. To bypass this "bottleneck," several strategies, such as functional imaging (9-11) and clinical prediction scores (12-15), have been proposed, but their success has been variable and inconsistent (12-15).

Thus far, the diagnostic accuracy of imaging has been investigated in only single-center surveys (14, 16-18) and in a meta-analysis (19). However, with few exceptions the studies did not follow the Standards for the Reporting of Diagnostic accuracy studies (20) in that they lacked an unambiguous diagnosis of unilateral PA as a reference. The only prospective, randomized study available reported no differences in the burden of antihypertensive medications

required to control blood pressure (BP) and the quality of life indexes, between a computed tomography (CT)-based and an AVS-based strategy to select patients for adrenalectomy (21), and therefore claimed the 2 strategies to be equivalent. However, only half the patients in each diagnostic strategy arm were adrenalectomized; thus, the study was underpowered to show significant outcome differences (22). Outcome equivalence of imaging- and AVS-based strategies was claimed in other small-sized studies that were affected by a selection bias due to their retrospective design (23, 24).

The Adrenal Vein Sampling International Study (AVIS-2) recruited PA patients, who underwent AVS in major referral centers of 4 continents, because they sought a surgical cure (25). A sizable proportion of the patients recruited underwent adrenalectomy, which was AVS-guided in the majority and based on clinical indications in a tiny subset. Hence, the presence of unilateral PA was conclusively established based on biochemical and/or clinical cure at follow-up. Moreover, the study was designed to collect information on imaging by CT and/or magnetic resonance (MR), as performed in a real-life practice setting in expert referral centers.

Using this large data set and this unambiguous postoperative diagnosis of unilateral PA, we investigated the hypothesis that imaging could allow an accurate detection of unilateral PA (20), and that imaging-positive PA patients might show a better clinical outcome post adrenalectomy than imaging-negative PA patients.

Materials and Methods

Study Population

The AVIS-2 study was conceived in 2012 as a large, multicenter registry of individual patients who underwent AVS studies worldwide. Per protocol and following the guidelines (4, 6), all patients were underwent AVS and, prior to it, had imaging by CT and/or MR, according to each center's practice as described in the supplementary material (26).

Recruitment ended in 2015; the database was locked January 15, 2017, after which only the follow-up data were gathered. Details of the methodology, the overall clinical outcomes in the AVIS-2 population, and the impact of different biochemical threshold values for assessing bilateral selectivity and lateralization, such as technical success and diagnostic yield, of AVS have been previously reported in detail (25, 27) and are briefly recapitulated here and in the supplementary material (26).

Inclusion and Exclusion Criteria

The participating centers were selected as described previously (25, 27). The patients' inclusion criteria were: a) age 18 years or older; b) the center's agreement to participate in data collection; and c) approval by the relevant institutional ethics committee. The unwillingness of the lead investigator to participate in the study and/or the lack of ethics committee approval were the exclusion criteria. For the present study a further exclusion entailed the lack of adequate imaging data. All procedures followed the principles of the Declaration of Helsinki, and the protocol of the study was approved by the institutional ethics committees.

Definitions and Assignment to Treatment

The gold-standard diagnostic reference used to evaluate the accuracy of imaging was unilateral PA. The latter was diagnosed in the patients who underwent unilateral laparoscopic adrenalectomy and showed full biochemical cure and/or complete cure of the high BP at follow-up at least 4 months after surgery. This definition is amongst the most rigorous used thus far for studies of the diagnostic accuracy of tests in PA.

Biochemical cure was defined as the normalization of plasma aldosterone concentration, aldosterone-renin ratio, and serum K^+ level post adrenalectomy (28), following the Primary Aldosteronism Surgery Outcome (PASO) criteria (29).

Cure of arterial hypertension was defined as BP values of less than 140 mm Hg systolic and less than 90 mm Hg diastolic without any antihypertensive treatment following the PASO criteria (29).

A sensitivity analysis was also undertaken using a looser definition of unilateral PA based on partial biochemical cure and a BP outcome entailing cure, marked improvement, and mild improvement, and described in the supplementary material (26).

Imaging and Adrenal Vein Sampling

Because this study aimed at depicting the diagnostic yield of imaging as undertaken in current real-life practice, and not in the setting of a centralized evaluation, imaging results were analyzed at each center by experienced radiologists.

Adrenal nodules were defined as nodular lesions with a diameter greater than 5 mm at imaging. This cutoff was chosen based on the results of a pilot study that showed that only nodules exceeding this size could be consistently detected when independently examined by different experienced radiologists (see the supplementary material) (26). Patients were defined as imaging positive or imaging

negative based on the presence or absence of a unilateral nodular lesion greater than 5 mm at imaging. Adrenal hyperplasia was not considered because of the high variability and lack of standardization for the recognition of this pathology at imaging.

Bilaterally selective (successful) AVS was defined as a selectivity index of 2.0 or greater under unstimulated conditions, and/or 4.0 or greater post cosyntropin (30) on both sides.

Lateralized PA was defined as a lateralization index on the dominant side of 2.0 or greater on a bilaterally successful AVS under unstimulated conditions, and/or 4.0 or greater post cosyntropin as described previously (25).

The allocation of patients to surgical or medical treatment was left to the discretion of the investigators at each participating center.

AVS-guided adrenalectomy was defined as surgery performed after bilaterally selective AVS showing lateralized aldosterone excess. Non–AVS-guided adrenalectomy was defined as surgery performed after nonbilaterally selective AVS results and/or a lateralization index below the threshold values in use at each center. The patients who showed no lateralization and those who were not cured biochemically after unilateral adrenalectomy were classified as bilateral PA.

BP outcomes were predetermined and categorized as cure, defined as in the PASO study (29), and also as marked improvement, mild improvement, and no improvement (Supplementary Table 1) (26).

Data Collection

Data were gathered with a predefined web-based platform and stored securely on a server at the coordinating center. Appropriate filters were applied to prevent input of values that were in the wrong units and/or biologically implausible. Anonymization of patient data was used to ensure privacy protection (available as supplementary material) (26), as described previously (25).

Data Handling and Statistical Analysis

After locking the database, before undertaking the statistical analysis the data were checked for internal consistency and harmonized to a standard format, as described (25). Univariate and multivariate outliers were identified using the procedure of Tabachnick and Fidell (31). Whenever the underlying reasons could not be clarified with the center's lead investigator, they were excluded from the analysis.

Results are expressed as mean ± SD, or median and interquartile range, as appropriate. Statistical significance was set at P less than .05. Continuous variables that showed a normal distribution at Kolmogorov-Smirnov test were analyzed with parametric tests. Appropriate data transformations and/or nonparametric tests (Wilcoxon) were used in case of a skewed distribution. The Pearson χ^2 test was used for analysis of categorical variables.

SPSS for Mac (version 27 for Mac, IBM-SPSS), Prism (version 9.1 for Mac, GraphPad Software), and MedCalc (MedCalc Software, version 15.8) were used for the statistical analysis.

Results

The patients were recruited in 19 centers on 4 continents comprising North America, Europe, Asia (including Japan), and Australia. At database locking, 1820 patients had been recruited, but it was decided to analyze only the studies performed from 2000 to 2015, to examine a cohort better reflecting current practice. This left a total of 1625 patients to be analyzed, of whom 558 were enrolled prospectively from 2013 to 2015, and 1067 were recruited retrospectively from 2012 to 2000. These groups showed no statistically significant differences of clinical features (see supplementary material) (26).

Although according to the protocol and guidelines all patients in the AVIS-2 study had undergone imaging prior to AVS (4, 6), information on the presence or absence of nodules and their size was available for only 81%, that is, 1311, of the total cohort of 1625 patients (Fig. 1).

Table 1 shows the demographic features of the patients with imaging data. The prevailing ethnicity was White (74% vs Asian 22%; African and African American 3%; and Hispanic 0.5%). The average age was 50.8 ± 11.0 years; 60% were men; the average body mass index was 28.3 ± 5.4; and obesity was common, with 35% of the patients having a body mass index greater than 30.0.

Imaging Results

Of the 1311 patients with full imaging data, 1142 patients (87%) underwent only CT, 101 (8%) only MR, and 68 (5%) both CT and MR; thus, 1210 patients had CT and 169 MR data (see Fig. 1).

The patients with imaging data did not differ from those of the whole AVIS-2 study population (25) with respect to age, sex, systolic and diastolic BP, heart rate, plasma renin activity, plasma aldosterone concentration, renin, aldosterone-renin ratio, and burden of antihypertensive medications (all P values were nonsignificant; Supplementary Table 5 and Supplementary Fig. 4) (26). A total of 178 additional patients were included in a sensitivity analysis (shown in the supplementary results) because information was available on only the presence, but not the size, of the nodules.

The rate of patients with exhaustive imaging was significantly higher after than before 2004 (Supplementary Fig.

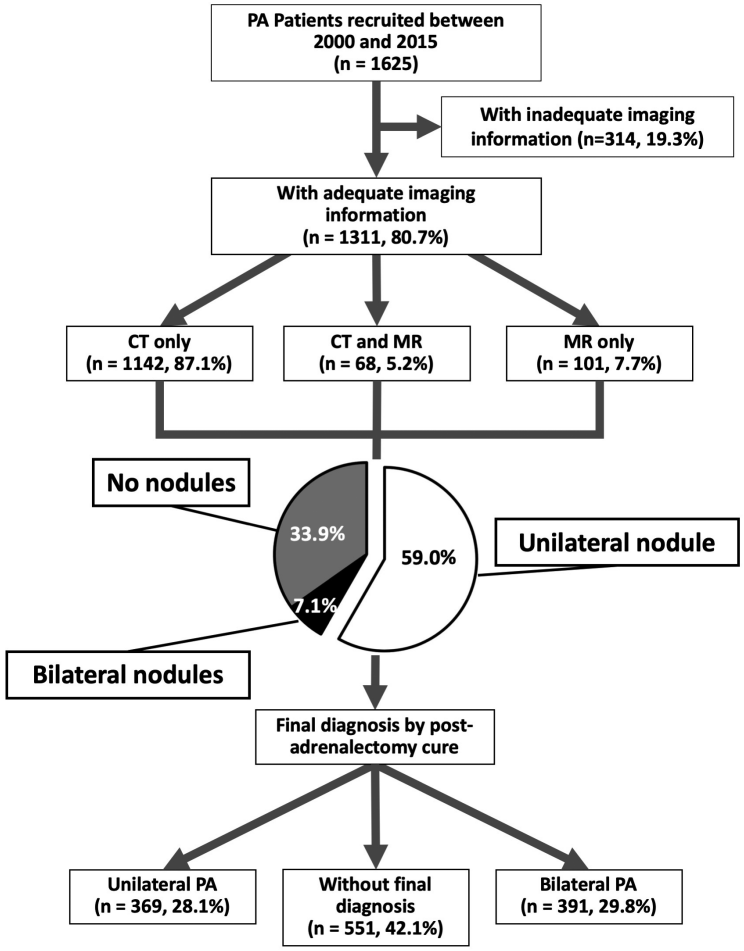

Figure 1. Flowchart of the Adrenal Vein Sampling International Study (AVIS-2)-IM study; the pie graph illustrates the results of imaging in the patients of AVIS-2-IM study. The final diagnosis was based on biochemical and/or full clinical cure post adrenalectomy and was used as a reference for establishing diagnostic accuracy.

5) (26), suggesting that imaging data were not fully reported in the early years of the study. Of note, full imaging data were available more often in patients of Asian ethnicity than in the other ethnic groups (see Supplementary Table 5) (26).

Importantly, 34% of the patients had no detectable adrenal nodules and 7% had bilateral nodules at imaging, indicating that the latter did not provide identification of a unilateral nodule in 41% of them. Nodules were detected more commonly (about 2-fold) on the left than the right side (39% vs 20%; $P < .001$).

CT and MR results were concordant in 63% in the small subset (n = 68) of patients submitted to both imaging techniques (Supplementary Table 6) (26).

Diagnostic Accuracy of Imaging for Identification of Unilateral Primary Aldosteronism

The imaging data and the final diagnosis of unilateral PA were available for 28% (369/1311); bilateral PA was judged to involve 30% (391/1311) of the cohort.

When patients were divided into left (n = 237) and right (n = 132) unilateral PA based on final diagnosis, a discordance with the adrenal side identified at imaging occurred in 28% of the patients (Table 2). In the 369 patients with unilateral PA, the diagnosis was missed at imaging in 22% (82/369), who had either no nodules (n = 67), or bilateral nodules (n = 15) (see Table 2).

If imaging alone had been used for subtype differentiation, these patients would have been denied a potentially curative operation; moreover, the removal of the wrong adrenal gland would have occurred in 6% (21/369) of the patients.

Culprit Nodule Size and Final Diagnosis

The size distribution of the nodules was skewed (see Fig. 2) at the Kolmogorov-Smirnov normality test ($P < .001$), with a median size of 14.0 mm (range, 5-60 mm).

The accuracy of imaging-detected nodules, and the nodule size that provided the best combination of sensitivity and specificity for identification of unilateral PA, was

estimated by the area under (AUC) the receiver operating characteristic (ROC) curve and Youden index analysis (Fig. 3). The ROC curve AUC was 0.636 (95% CI, 0.584-0.686), which was significantly ($P = .006$) higher than the identity line AUC, indicating that the detection of a unilateral nodule carries a 13% diagnostic gain over tossing a coin.

The nodule size associated with the highest diagnostic accuracy at Youden index analysis was 16 mm (95% CI, 12.0-21.0 mm), which provided a specificity of 82% (95% CI, 64%-93%) but a low sensitivity of 43% (95% CI, 37%-48%).

However, the nodule identified at imaging was contralateral to the adrenalectomy side in 6% (21/287) of the PA patients who had a single nodule and a surgically cured unilateral disease, a rate that raised to 12% (36/302) by considering the largest nodules in those with bilateral nodules.

Table 1. Baseline demographic, clinical, and biochemical features of the 1311 primary aldosteronism patients with imaging data available

Variable	Value
Age, y	50.8 ± 11.0
Sex (M/F), No., %	782 (59.6%)/529 (40.4%)
Body mass index	28.3 ± 5.4
Systolic BP, mm Hg	152 ± 20
Diastolic BP, mm Hg	92 ± 13
Heart rate, beats/min	73 ± 12
Serum K^+, mmol/L	3.6 ± 0.5
DRC, mIU/L	2.46 (1.64-4.92)
PAC, ng/dL	22.7 (14.3-36.5)
ARR, ng/dL/ng/mL/h	67.5 (36.3-121.0)
Ethnicity, %	
White	74.1
Asian	22.4
African	3.1
Hispanic	0.5

Mean ± SD or median and interquartile range.
Abbreviations: ARR, aldosterone renin ratio; BP, blood pressure; DRC, direct renin concentration; F, female; M, male; PAC, plasma aldosterone concentration.

Clinical Outcome in Imaging-Positive and -Negative Patients

Of the PA patients with full imaging data, only 2% showed no improvement in BP control with unilateral adrenalectomy, while 39% were cured of arterial hypertension, and 44% and 14% exhibited a marked and a mild improvement, respectively.

On the whole, the clinical outcome, that is, the proportion of cured, markedly improved, and mildly improved cases,

Table 2. Concordance between imaging findings and final diagnosis of unilateral primary aldosteronism (PA)

Cross-sectional imaging diagnosis, No., %	Final diagnosis, No. (%)		
	Right unilateral PA	Left unilateral PA	Total
Right nodule	83 (22.5%)	6 (1.6%)	89 (24.1%)
Left nodule	15 (4.1%)	183 (49.6%)	198 (53.7%)
Bilateral nodules	8 (2.2%)	7 (1.9%)	15 (4.1%)
No nodules	26 (7.1%)	41 (11.1%)	67 (18.2%)
Total	132 (35.8%)	237 (64.2%)	369 (100.0%)

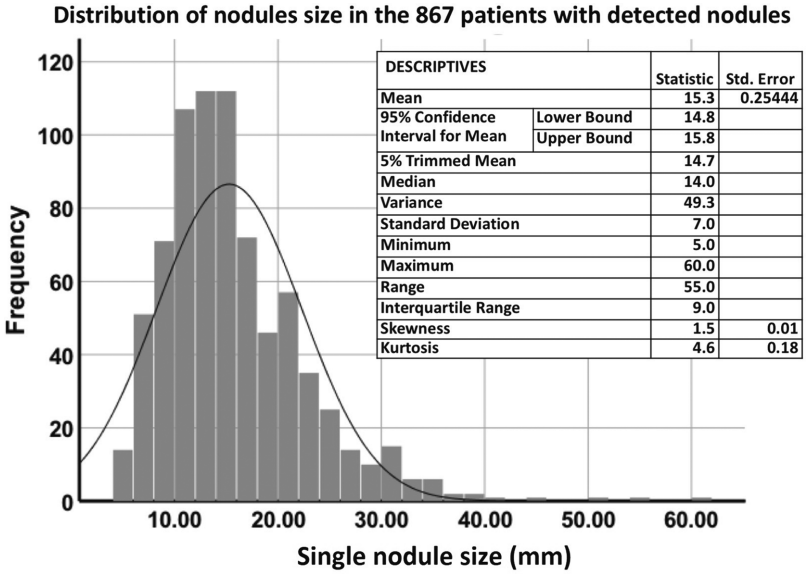

Figure 2. Distribution of size of the nodules identified by computed tomography and/or magnetic resonance imaging in the Adrenal Vein Sampling International Study (AVIS-2)-IM study population. The summary statistics are presented in the embedded table.

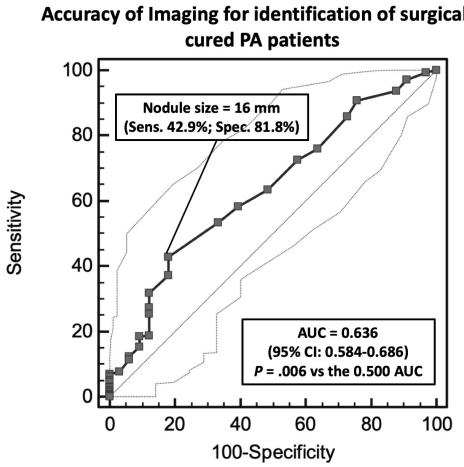

Figure 3. The receiver operating characteristic curve analysis was performed to determine the usefulness of the nodule size, as determined at imaging, for the identification of unilateral primary aldosteronism (PA), that is, the patients biochemically/clinically cured after unilateral adrenalectomy. The area under the curve (AUC), which estimates overall accuracy, was significantly higher than that under the identity line indicating that the detection of a nodule provided an increase of diagnostic gain over tossing a coin. At Youden index analysis the nodule size associated with the best combination of sensitivity and specificity was 16 mm.

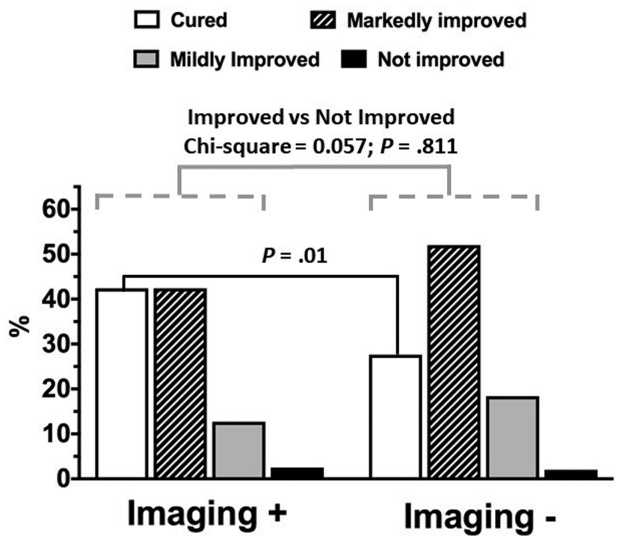

Figure 4. The graph shows the distribution of blood pressure outcome in the primary aldosteronism patients who underwent unilateral adrenalectomy divided into those who were imaging positive (Imaging +) and those who were imaging negative (Imaging –).

did not differ significantly between the imaging-positive and imaging-negative patients (chi-square = 0.057; $P = .811$). In the former patients, elevated BP was cured in 42%, markedly improved in 42%, mildly improved in 13%, and not improved in 2%. The corresponding figures for imaging-negative patients were 28%, 52%, 18%, and 2% (Fig. 4).

Stratification of the patients by AVS-guided and non–AVS-guided adrenalectomy showed no significant differences between imaging-positive and imaging-negative patients.

Of the cured patients, 26% had a nondiagnostic or a negative AVS; of these, 28% showed no nodules at imaging and 4% had bilateral nodules.

Among those with positive imaging, the mean size of nodules did not differ significantly between the AVS-guided and non–AVS-guided adrenalectomy groups (14.7 ± 6.7 mm vs 15.6 ± 7.2 mm; $P = .143$), but the cure rate was higher in the imaging-positive than in the imaging-negative patients at a post hoc comparison procedure that eliminates type 1 error (https://www.youtube.com/watch?v=Rp0qorrPXA0“\l “t=399.41984921).

Discussion

This study was conceived to capture real-life practice in subtyping of PA in a large population of patients seeking surgical cure and, therefore, referred to leading centers on 4 continents to undergo AVS. Therefore, even though the choice of treatment was left to each participating center, based on local guidelines and a holistic evaluation of each patient, the majority of the patients were allocated to medical treatment or surgery based on AVS results. However, this explains why some patients with unilateral PA at AVS did not receive surgery, and vice versa.

The first remarkable finding of this study was that imaging did not detect adrenal nodules in 34% of the PA patients and, moreover, showed bilateral nodules in 7% of them (see Fig. 1). Thus, the culprit adrenal lesion could not be identified with imaging in about 4 out of 10 of the cases, in a selected population of patients with a florid PA phenotype.

Of note, as recommended by all current guidelines, the strategy that was exploited in the AVIS-2 Study required adrenal imaging only after PA had been biochemically ascertained. This study showed that use of imaging upstream in the diagnostic flowchart would have caused the denial of the correct diagnosis and treatment to one-third of the PA patients, thus providing strong support for the guideline recommendation. Moreover, use of imaging upstream in the diagnostic algorithm would result in a high rate of false positives, owing to the high prevalence of adrenal nodules in hypertensive patients with aging (32, 33), and the fact that most adrenal nodules are not hormonally active, that is, they comprise incidentalomas (32, 33). Thus, we herein showed that on the one hand, adrenal nodules were not a prerequisite for PA; on the other hand, they are common and may not represent an aldosterone-producing adenoma, particularly in older patients.

A conclusive diagnosis of unilateral PA, which was confirmed at follow-up post adrenalectomy by the most stringent criteria available, was eventually made in 28% of the PA patients in AVIS-2. Hence, we could evaluate the diagnostic accuracy of imaging using the area under the ROC

curve, based on this diagnostic gold-standard reference. This area was 0.636, which corresponded to a small, although significant, diagnostic gain over tossing a coin (Fig. 3).

The nodule diameter that performed best for identification of the adrenal lesion and of unilateral PA was 16 mm (95% CI, 12.0-21.0 mm), a size greater than the 10 mm cutoff endorsed by the Endocrine Society guidelines as the cutoff for distinguishing between macroadenoma and microadenoma (4) and used in a clinical prediction score for identifying unilateral PA (12). This nodule size carried only a 43% sensitivity, but an 83% specificity, indicating that about 1 every 5 patients would obtain a false-negative result if this size criterion were used to identify the aldosterone-producing nodule.

For PA subtyping, concordance between the side of the unilateral adrenal lesion on imaging and the side of confirmed aldosterone-producing adenoma was observed in only 266, that is 72%, of the 369 patients (see Table 2). Hence, based on imaging alone, 22% (82/369) of patients whose imaging was negative would have been precluded potentially curative surgery, and a further 6% (21/369) would have undergone removal of the wrong adrenal.

Of note, among the surgically cured patients, more than a quarter had a nondiagnostic or a negative AVS. Moreover, imaging did not identify the responsible adrenal in about 40% of them. Hence, neither a negative/nondiagnostic AVS, nor no or bilateral nodules at imaging could exclude the possibility of long-term cure.

AVIS-2-Imaging (AVIS-2-IM) has limitations and strengths that need to be acknowledged. First, extrapolation of these results to the general population of PA patients could be limited because the study design allowed recruitment of a selected cohort of PA patients comprising the most florid PA phenotypes. Second, caution is advised before generalizing the results, because White individuals were overrepresented compared to individuals of other ethnicities in AVIS-2-IM and, moreover, patients of African origin were few. Third, it could be argued that the study might have been affected by selection biases due to changes in clinical practice over time, because data were retrieved retrospectively from 2012 to 2000, and prospectively, from 2012 to 2015. This possibility seems, however, unlikely given that the clinical and imaging features did not differ between the retrospective and prospective cohort. The lack of centralization for the reading of imaging might also be perceived as a limitation; instead, in our view, it was a strength of the study, because it provided a snapshot of real-world clinical practice on imaging in PA. Moreover, our conclusions have been derived from a proportion (58%) of the 1311 patients from the AVIS-2 database, for whom the final diagnosis data were available. While this can be regarded as a limitation, we consider it a strength because these patients received an unambiguous diagnosis of PA subtype.

Finally, a limitation that is common to practically all studies in this field needs to be acknowledged: because of the lack of accepted criteria to conclusively diagnose bilateral PA, which is feasible only for the familial forms of PA, it might be that some patients labeled as having bilateral PA in reality had a unilateral form.

All these potential limitations are counterbalanced by 2 major points of strength: i) a large dataset of PA patients carefully subtyped by AVS and evaluated after surgery; and ii) use of a conclusive diagnosis of unilateral disease as a gold-standard reference.

In summary, this study showed for the first time in a large, multiethnic cohort of PA patients that, even in the most experienced hands, imaging did not provide an accurate detection of PA in general and, even more so, of unilateral PA. This information has at least 5 important practical implications: i) the finding of no, or of bilateral, nodules at adrenal imaging by no means excludes the diagnosis of unilateral surgically curable PA; ii) if the clinical decision making were based on imaging results alone, more than 40% of the patients would be judged not to have a unilateral form of PA and, therefore, would be denied potentially curative surgery; iii) in the adrenalectomized patients, who were conclusively diagnosed as having unilateral PA, and for whom imaging was available, the diagnosis was missed in 22% as imaging showed either no nodules (in 18%) or bilateral nodules (in 4%); iv) unnecessary adrenalectomies would have been undertaken in 6% of the patients if imaging had been used for clinical decision making (see Table 2); and v) negative adrenal imaging does not imply a worse clinical outcome following AVS-guided adrenalectomy (see Fig. 4).

Considering that AVS is the "bottleneck" in the management of PA patients and the diagnostic performance of imaging herein documented, future studies need to seek alternative strategies for selecting candidates for surgery. In this context, functional imaging with radiotracers in positron emission tomography/CT or positron emission tomography/MR looks much promising, but thus far, the very short half-life of the C11 radiotracers used has confined clinical use of this technique to only a few centers endowed with a cyclotron on site (9-11, 34). Longer half-life radiotracers might eventually furnish a powerful diagnostic tool, particularly for centers that have no access to AVS (35, 36).

Acknowledgments

Financial Support: This work was supported by FORICA (The Foundation for Advanced Research in Hypertension and Car-

diovascular Diseases) and the Società Italiana dell'Ipertensione Arteriosa (to G.P.R.); the Else Kröner-Fresenius-Stiftung (to M.R.); the Deutsche Forschungsgemeinschaft (DGE, the German Research Foundation, No. 314061271-TRR 205 to A.R., M.R., and J.D.); the Japan Agency for Medical Research and Development (AMED) (grant No. JP20ek0109352 to M.N.); and the National Center for Global Health and Medicine, Japan (grant No. 27-1402, 30-1008 to A.T.).

Clinical Trial Information: AVIS registration at clinicaltrials.gov number NCT01234220 (registered 4 November 2010).

Author Contributions: G.P.R., F.C., and M.B. conceived the study. G.P.R. and F.C. managed the data and conducted the statistical analysis. G.P.R. drafted the manuscript. All the authors collaborated in data collection, interpretation of the results, and revision of the manuscript. All authors have read and approved the manuscript.

Additional Information

Correspondence: Gian Paolo Rossi, MD, Internal & Emergency Medicine & Specialized Hypertension Center, Department of Medicine, DIMED, University Hospital via Giustiniani 2, 35126 Padova, Italy. Email: gianpaolo.rossi@unipd.it.

Disclosures: The authors have nothing to disclose.

Data Availability: Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Rossi GP, Bernini G, Caliumi C, et al; PAPY Study Investigators. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006;**48**(11):2293-2300.
2. Xu Z, Yang J, Hu J, et al; Chongqing Primary Aldosteronism Study (CONPASS) Group. Primary aldosteronism in patients in China with recently detected hypertension. *J Am Coll Cardiol*. 2020;**75**(16):1913-1922.
3. Monticone S, Burrello J, Tizzani D, et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. *J Am Coll Cardiol*. 2017;**69**(14):1811-1820.
4. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;**101**(5):1889-1916.
5. Nishikawa T, Omura M, Satoh F, et al; Task Force Committee on Primary Aldosteronism, The Japan Endocrine Society. Guidelines for the diagnosis and treatment of primary aldosteronism—the Japan Endocrine Society 2009. *Endocr J*. 2011;**58**(9):711-721.
6. Rossi GP, Bisogni V, Bacca AV, et al. The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism. *Int J Cardiol Hypertens*. 2020;**5**:100029.
7. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;**71**(19):e127-e248.
8. Rossi GP, Barisa M, Allolio B, et al. The Adrenal Vein Sampling International Study (AVIS) for identifying the major subtypes of primary aldosteronism. *J Clin Endocrinol Metab*. 2012;**97**(5):1606-1614.
9. Burton TJ, Mackenzie IS, Balan K, et al. Evaluation of the sensitivity and specificity of (11)C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn's adenomas. *J Clin Endocrinol Metab*. 2012;**97**(1):100-109.
10. O'Shea PM, O'Donoghue D, Bashari W, et al. ^{11}C-Metomidate PET/CT is a useful adjunct for lateralization of primary aldosteronism in routine clinical practice. *Clin Endocrinol (Oxf)*. 2019;**90**(5):670-679.
11. Soinio M, Luukkonen AK, Seppänen M, et al. Functional imaging with 11C-metomidate PET for subtype diagnosis in primary aldosteronism. *Eur J Endocrinol*. 2020;**183**(6):539-550.
12. Küpers EM, Amar L, Raynaud A, Plouin PF, Steichen O. A clinical prediction score to diagnose unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2012;**97**(10):3530-3537.
13. Riester A, Fischer E, Degenhart C, et al. Age below 40 or a recently proposed clinical prediction score cannot bypass adrenal venous sampling in primary aldosteronism. *J Clin Endocrinol Metab*. 2014;**99**(6):E1035-E1039.
14. Umakoshi H, Tsuiki M, Takeda Y, et al; JPAS Study Group. Significance of computed tomography and serum potassium in predicting subtype diagnosis of primary aldosteronism. *J Clin Endocrinol Metab*. 2018;**103**(3):900-908.
15. Wu CH, Wu V, Yang YW, et al; TAIPAI group. Plasma aldosterone after seated saline infusion test outperforms captopril test at predicting clinical outcomes after adrenalectomy for primary aldosteronism. *Am J Hypertens*. 2019;**32**(11):1066-1074.
16. 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**(3):1066-1071.
17. Sarlon-Bartoli G, Michel N, Taieb D, et al. Adrenal venous sampling is crucial before an adrenalectomy whatever the adrenal-nodule size on computed tomography. *J Hypertens*. 2011;**29**(6):1196-1202.
18. Lingam RK, Sohaib SA, Vlahos I, et al. CT of primary hyperaldosteronism (Conn's syndrome): the value of measuring the adrenal gland. *AJR Am J Roentgenol*. 2003;**181**(3):843-849.
19. Kempers MJE, Lenders JWM, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann Intern Med*. 2009;**151**(5):329-337.
20. Bossuyt PM, Reitsma JB, Bruns DE, et al; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;**351**:h5527.
21. Dekkers T, Prejbisz A, Kool LJS, et al; SPARTACUS Investigators. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial. *Lancet Diabetes Endocrinol*. 2016;**4**(9):739-746.
22. Rossi GP, Funder JW. Adrenal venous sampling versus computed tomographic scan to determine treatment in primary aldosteronism (the SPARTACUS Trial): a critique. *Hypertension*. 2017;**69**(3):396-397.
23. Thiesmeyer JW, Ullmann TM, Stamatiou AT, et al. Association of adrenal venous sampling with outcomes in primary aldosteronism for unilateral adenomas. *JAMA Surg*. 2021;**156**(2):165-171.

24. Ma D, Liu X, Zeng L, et al. The role of adrenal venous sampling and computed tomography in the management of primary aldosteronism. *J Hypertens*. 2021;**39**(2):310-317.
25. Rossi GP, Rossitto G, Amar L, et al. Clinical outcomes of 1625 patients with primary aldosteronism subtyped with adrenal vein sampling. *Hypertension*. 2019;**74**(4):800-808.
26. Rossi GP, Crimi F, Rossitto G, et al. *Supplemental data for: Identification of Surgically Curable Primary Aldosteronism by Imaging in a Large Multiethnic International Study*. doi:10.25430/researchdata.cab.unipd.it.00000369. http://researchdata.cab.unipd.it/369/. Date of upload: March 30, 2021.
27. Rossitto G, Amar L, Azizi M, et al. Subtyping of primary aldosteronism in the AVIS-2 Study: assessment of selectivity and lateralization. *J Clin Endocrinol Metab*. 2020;**105**(6):2042-2052.
28. Seccia TM, Caroccia B, Gomez-Sanchez EP, Gomez-Sanchez CE, Rossi GP. The biology of normal zona glomerulosa and aldosterone-producing adenoma: pathological implications. *Endocr Rev*. 2018;**39**(6):1029-1056.
29. Williams TA, Lenders JWM, Mulatero P, et al; Primary Aldosteronism Surgery Outcome (PASO) investigators. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol*. 2017;**5**(9):689-699.
30. Rossi GP, Auchus RJ, Brown M, et al. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. *Hypertension*. 2014;**63**(1):151-160.
31. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. 4th ed. Allyn & Bacon; 2001. ISBN 0-321-05677-9. Hardcover.
32. Ichijo T, Ueshiba H, Nawata H, Yanase T. A nationwide survey of adrenal incidentalomas in Japan: the first report of clinical and epidemiological features. *Endocr J*. 2020;**67**(2):141-152.
33. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study group on adrenal tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab*. 2000;**85**(2):637-644.
34. Bongarzone S, Basagni F, Sementa T, et al. Development of [^{18}F]FAMTO: a novel fluorine-18 labelled positron emission tomography (PET) radiotracer for imaging CYP11B1 and CYP11B2 enzymes in adrenal glands. *Nucl Med Biol*. 2019;**68-69**:14-21.
35. Abe T, Naruse M, Young WF, et al. A novel CYP11B2-specific imaging agent for detection of unilateral subtypes of primary. *J Clin Endocrinol Metab*. 2016;**101**(3):1008-1015.
36. Ding J, Zhang Y, Wen J, et al. Imaging CXCR4 expression in patients with suspected primary hyperaldosteronism. *Eur J Nucl Med Mol Imaging*. 2020;**47**(11):2656-2665.