Subtyping of Primary Aldosteronism in the AVIS-2 Study: 
Assessment of Selectivity and Lateralisation

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Running title: Selectivity and Lateralisation of adrenal vein sampling

Words count: abstract: 250; body of text 3334; refs: 30; Figs 5; Tabs. 2

Keywords: aldosterone; endocrine hypertension; primary aldosteronism; hyperaldosteronism subtyping; diagnosis; adrenal vein sampling; lateralisation: selectivity.

The AVIS was registered at clinicaltrials.gov number NCT01234220

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All authors have read and approved the manuscript. There is no conflict of interest and financial disclosure to be disclosed.
Abstract (250)

**Background:** The outcome of adrenal venous sampling (AVS), the key test for subtyping primary aldosteronism (PA), is suboptimal with the widely criteria for its performance and interpretation.

**Methods:** In the AVIS-2, a multi-centre international study involving tertiary referral centres worldwide, which created the largest registry of individual AVS data, we investigated how predefined homogeneous cut-off values of the selectivity (SI) and lateralisation index (LI) affected rate of bilateral success, identification of unilateral aldosteronism and blood pressure outcomes.

**Findings:** AVIS-2 involved 1625 individual AVS studies performed between 2000 and 2015 in 19 centres located in four continents. We found that under unstimulated conditions, the rate of bilateral AVS success progressively decreased with increasing SI cut-offs. Furthermore, with currently used LI cut-offs the rate of lateralised PA leading to adrenalectomy was as low as < 25%. A within-patient pairwise comparison of 402 AVS performed both under unstimulated conditions and cosyntrropin-stimulation showed that high SI cut-off values displayed suboptimal sensitivity and/or specificity for determining AVS success. Compared to unstimulated AVS, cosyntrropin increased bilateral selectivity rates for SI cut-offs ≥ 2·0, but reduced lateralisation rates (p < 0·001). Post-adrenalectomy outcomes were not ameliorated by use of cosyntrropin or more restrictive diagnostic criteria.

**Interpretation:** Commonly used SI and LI cut-offs are associated with disappointingly low rate of AVS success and identification of unilateral primary aldosteronism. Use of evidence-based protocols and less restrictive cutoffs can ameliorate the clinical use of this costly and invasive test.

**Funding:** This study was supported in part by research grants to GPR from FORICA (The FOundation for advanced Research In Hypertension and CArdiovascular diseases) and the
Società Italiana dell’Ipertensione Arteriosa and from the Else Kröner-Fresenius-Stiftung to M.R.
INTRODUCTION

Primary aldosteronism (PA) is often undetected, because regarded as a rare condition, while instead it is the most common cause of endocrine arterial hypertension.\textsuperscript{1-4} Failure to early identify and subtype PA leaves a multitude of patients exposed to life-long hyperaldosteronism, and thus to cardiovascular events, particularly atrial fibrillation, as shown in both retrospective and prospective studies.\textsuperscript{5-8} In the work-up of PA patients, the subtyping is a fundamental step because patients with a unilateral form, mostly aldosterone-producing adenoma (APA) and unilateral adrenal hyperplasia,\textsuperscript{9,10} need unilateral laparoscopic adrenalectomy to obtain definitive correction of the hyperaldosteronism and often cure of arterial hypertension. At variance, patients with bilateral PA, predominantly bilateral adrenal hyperplasia (BAH, also known as idiopathic hyperaldosteronism, IHA), require life-long medical treatment with a mineralocorticoid receptor antagonist (MRA), alone but more often in combination with multiple other antihypertensive agents.

To distinguish between unilateral and bilateral PA, all current guidelines advocate use of adrenal vein sampling (AVS),\textsuperscript{11,12} a technically demanding and prone to failure test, with success defined as accomplishment of bilaterally selectivity, i.e. adequate bilateral sampling of adrenal blood. Estimation of selectivity also serves to minimize the impact of two potential confounders when ascertaining lateralisation of aldosterone excess, i.e. for the degree of proximity of the catheter’s tip to the adrenal cortex, and for blood dilution from accessory veins or inferior vena cava blood.

The criteria to define selectivity and lateralisation remain, however, quite variable, even at major tertiary centres where AVS is performed on a regular basis, as shown by summary AVS information from a large international survey (AVIS-1),\textsuperscript{13} and by independent expert consensus documents.\textsuperscript{14,15} This heterogeneity can have a profound effect on the clinical decision-making and thus on the outcome of AVS.
The Adrenal Vein sampling International Study (AVIS)-2 was planned after publication of AVIS-1 with the aim of creating a large registry of individual AVS data. The results of this study regarding clinical outcomes, i.e. correction of aldosteronism and rate of cured/improvement of arterial hypertension, based on centre-defined criteria, are reported elsewhere (Companion paper). They highlighted the current suboptimal outcomes of AVS in a large population of PA patients seeking surgical cure with no other preselection criteria, thus depicting real-life clinical practice. Based on those findings, in this study we wished to explore the impact of more standardized and homogeneous criteria on management of PA patients and AVS outcomes. Hence, we herein report on: i) the rate of selective AVS studies, ii) the rate of ascertained unilateral PA leading to adrenalectomy; iii) the post adrenalectomy blood pressure outcomes as a function of the AVS protocol and of commonly advocated diagnostic cut-offs for the indexes defining selectivity (SI) and lateralisation (LI).

METHODS

The study rationale and design, centre selection, inclusion/exclusion criteria and whole data collection, including population characteristics and outcome analysis of AVIS-2 were reported in a separate paper and are recapitulated in the Supplemental Methods.

In brief, anonymized hormonal data from individual AVS studies were entered by local investigators in a dedicated web-based platform (https://fm.dmcs.unipd.it; data collection form available as Supplemental material). Investigators were requested to enter the units of measure as per local practice to avoid any conversion errors. Post-hoc harmonization to Conventional Units was undertaken in the final database. After database locking, data were checked for internal consistency and standing queries were clarified with centres’ lead investigators. The definition of the AVS indexes, including the relative aldosterone secretion index (RASI) has already been reported and is summarised in the Supplemental Table 2.
The diagnostic impact of different cut-off values for SI and LI on AVS data obtained with different AVS protocols (unstimulated or stimulated) was explored in the entire cohort. Selectivity and lateralisation analysis for these cut-offs were focused on guidelines-recommended,\textsuperscript{11,19} and/or expert consensus-endorsed values.\textsuperscript{14,15}

A paired within-patient, within-AVS comparison was conducted for cases with available pre and post-cosyntropin results. ROC (Receiver operating characteristic) curve analyses were performed to assess the performance of SI cut-off values obtained under unstimulated conditions ($SI_{\text{unstimulated}}$) using post-cosyntropin selectivity, defined as a $SI_{\text{cosyntropin}}$ cut-off = 5·0, as reference standard. By doing so and using Youden index, we identified the optimal cut-off value for $SI_{\text{unstimulated}}$, i.e. the best trade-off of sensitivity and specificity. This cut-off value was then compared with the currently recommended values.

As SI, LI, and RASI showed a non-normal distribution at Kolmogorov-Smirnov test (KS), their values are reported as median and interquartile range (IQR) and comparison across groups was performed with nonparametric Wilcoxon test. Frequency of categorical variables were analysed with Pearson’s $\chi^2$; McNemar’s test was used for comparison between different diagnostic criteria/cut-off within the same population. Significance was set at $p<0.05$. SPSS for Mac (vers. 24 for Mac, IBM-SPSS Bologna, Italy), GraphPad, Prism (vers. 6·00 for Mac, GraphPad Software, La Jolla California USA), and MedCalc (MedCalc Software Ostend Belgium, vers. 15·8) softwares were used for the statistical analysis.
RESULTS

Study population

Upon locking, the database comprised 1820 individual AVS data from consecutive patients studied in 19 centres. However, to obtain information on current AVS practice, it was decided to exclude the oldest studies and to limit the analysis to 1625 individual AVS studies performed from 2000 to 2015, as summarized in Figure 1. The clinical/demographic features of the PA patient population were reported in detail elsewhere\textsuperscript{16} and are recapitulated in the Supplemental Results (Supplemental Table 3).

AVS were performed under unstimulated conditions in 1274 (78·4\%) of the patients; pharmacologic stimulation was performed in 865 (53·2\%) cases: 85·8\% with cosyntropin, and in the rest with metoclopramide, which was used only in the coordinating centre. The results obtained with this drug are reported here only for comparison with the cosyntropin-stimulated AVS, because detailed analyses of the effect of metoclopramide on SI and LI have already been published.\textsuperscript{18,20}

AVS was performed under both unstimulated and cosyntropin-stimulated conditions in 402 patients (24·7\% of the total), which furnished the opportunity for a paired within-patient-within-AVS comparison in the largest cohort ever reported.

Rate of selectivity at different SI cut-off values

\textit{Unstimulated AVS}

The analysis of the rate of right, left, and bilateral selectivity showed that, under unstimulated conditions, increasingly higher cut-off values of the SI up to 5·0 results into a progressive fall of the rate of selective studies on each side and bilaterally (Figure 2 and supplemental Table 4). With the most stringent cut-off of 5·0, only 38·3\% of the studies were bilaterally selective; the rate raised to 67·3\% and 52·4\%, respectively, with the commonly used cut-offs values of 2·0 and 3·0.
Post-cosyntropin stimulated AVS

At variance with the fall observed with increasingly restrictive cutoffs under unstimulated conditions or during metoclopramide stimulation (Figure 2 and supplemental Figure 1), at more restrictive cut-off values the rate of selective studies was higher with cosyntropin than under unstimulated conditions. Moreover, it levelled with increasing cut-off values: the rate of selectivity decreased only by 9%, i.e. from 90·2% at a cut-off of 1·1, to 81·3% at 5·0. Noteworthy, the currently recommended SI cut-off value for cosyntropin-stimulated AVS of 5·0 \textsuperscript{11,15} was associated with a higher rate of bilaterally selective studies than under unstimulated conditions using any SI cut-off values \( \geq 2·0 \) (Figure 2 and Supplemental Table 4).

Use of intraprocedural cortisol assay

The intra-procedural rapid cortisol assay (IRCA) was used to confirm AVS selectivity under unstimulated conditions in two centres for a total of 178 patients. The use of IRCA was associated with higher rates of selectivity at each SI cut-off value (Supplemental Table 5).

Comparison of the IRCA cohort with cosyntropin-stimulated AVS showed a similar rate of bilateral selectivity for low SI cut-offs and a better performance of the latter only at SI cut-off values \( \geq 3·0 \) (Supplemental Table 5).

Comparison of unstimulated vs stimulated AVS: optimal unstimulated SI cut-off

The within-patient within-AVS pairwise comparison of unstimulated and post-cosyntropin data confirmed increased values of both SI and selectivity rate bilaterally after stimulation (Figure 3). Noteworthy, the SI values after cosyntropin (Supplemental Figure 2) showed a bimodal distribution, i.e. a clear-cut separation of selective and non-selective studies, that was demarcated by the currently recommended post-cosyntropin SI value cut-off of 5·0.\textsuperscript{11,15}
We used this value as a reference to define selectivity, in a ROC curve analysis to explore the diagnostic performance of unstimulated SI values in this cohort. This showed that on the whole unstimulated SI values provided a reasonable accuracy (AUC 0·756 (0·724-0·785), p < 0·0001 vs 0·50). Practically identical results (not shown) were obtained with an SI of 4·0, another popular post-cosyntropin cut-off, as reference. At Youden Index analysis, the SI cut-off that under unstimulated conditions offered the highest accuracy, i.e. a combination of 62% sensitivity and 92% specificity, was > 1·4 (Figure 3, Supplemental Table 6). When applied to the entire AVIS-2 database this cut-off furnished a rate of selectivity under unstimulated conditions similar to a post-cosyntropin SI cut-off > 5·0, regardless of IRCA being used or not (Figure 2, Supplemental Table 2).

Impact of diagnostic indexes on rate of ascertained lateralisation and adrenalectomy

Achievement of bilateral selectivity is a prerequisite to determine if the patient has a unilateral or a bilateral form of PA, i.e. for clinical use of AVS data. We therefore assessed the rate of lateralised patients, as defined by LI cut-off values ranging between 2·0 and 5·0,11,14,15 according to achievement of bilateral selectivity, as defined by use of (less or more restrictive) SI cut-off values of 1·4, 2·0, and 3·0 for unstimulated conditions, and 5·0 post-cosyntropin. To evaluate the impact of these different criteria on AVS outcome, this analysis involved 1004/1274 unstimulated, and 637/724 cosyntropin-stimulated AVS, who had full data on indication to, and performance of, adrenalectomy. This showed that the rate of lateralization, and of bilaterally selective studies, dropped significantly with adoption of higher SI cut-offs and with each unit increase in LI cut-off (Figure 4 and Supplemental Table 7). With commonly used cut-offs under unstimulated and cosyntropin-stimulated conditions, i.e. SI = 2·0 + LI = 3·0 and SI = 5·0 + LI = 4·0, the proportion of lateralising patients was 39·8% and 36·6%, respectively, (p = 0·174). It increased up to 55·6% (p < 0·001) with lower cut-offs for unstimulated SI and/or LI, as the 1·4 SI cut-off for selectivity (identified in the
paired analysis described above, combined with a cut-off of 2.0 for lateralisation. Overall lateralisation rates from the entire AVIS-2 dataset are shown in Supplemental Figure 3. Importantly, similar trends were observed for the rate of patients submitted to adrenalectomy based on the same AVS criteria, down to a nadir of 25% (Figure 4 and Supplemental Table 7). Of note, with increasingly stringent diagnostic cut-off values or with use of cosyntropin the relative proportion of adrenalectomized patients among those with lateralised AVS increased markedly (Figure 4 and Supplemental tab 7).

**Impact of cosyntropin on the assessment of lateralisation**

On the whole, after cosyntropin stimulation, notwithstanding the higher rate of bilaterally selective AVS studies with all commonly used cut-offs, a relatively lower proportion of patients was judged to have a lateralised form of PA (Figure 4 and Supplemental tab 7).

A pair-wise comparison of the bilaterally selective AVS under both unstimulated and cosyntropin-stimulated conditions showed a highly significant (p<0.001) fall of the LI values from baseline to post-cosyntropin, a finding confirmed in the sub-cohort of those who had a unilateral form of PA, as unambiguously established by biochemical cure at follow-up post-adrenalectomy (n=149/402).

By calculating the “central/peripheral ratio” originally introduced by Espiner E.A. et al, which some of us (GR, GPR) renamed relative aldosterone secretion (RASI) and proposed to dissect the contribution of the culprit and non-culprit adrenal to the LI value,\(^{18,21,22}\) we could clarify that the LI decreased because of a more prominent drop in the dominant than the non-dominant side (Table 1). This fall did not occur during metoclopramide stimulation (Supplemental Figure 4) and therefore was specific to cosyntropin.

A sensitivity analysis performed by excluding stepwise each individual centre showed similar results (Supplemental Table 4). In line with these findings and regardless of the LI cut-off used, the number of cases judged to be lateralised post-cosyntropin decreased significantly
from baseline (Table 2). Accordingly, the proportion of PA patients with unstimulated lateralised AVS results, but with post-cosyntropin AVS results indicating bilateral PA, was found to raise and could exceed 30% depending on the diagnostic criteria used (grey shaded cells, Table 1).

Impact of diagnostic indexes on blood pressure outcome

The relative distribution of blood pressure outcomes (no improvement; cure; and improvement, i.e. marked or mild, to allow comparison with current PASO consensus criteria – please see Supplemental Table 1) was found to be remarkably similar by the different diagnostic criteria or protocols used (Supplemental Figure 5). However, as a result of lower number of patients fulfilling lateralisation criteria and thus indication to surgery, their rate decreased progressively with use of the more restrictive LI cut-offs (Figure 5).

Importantly, in the “paired” cohort with lateralisation under unstimulated conditions, but no lateralization post-cosyntropin AVS, only a minority of the patients received adrenalectomy (Supplemental Table 9). Although this limited the statistical power of post-adrenalectomy outcome analysis, it is worth emphasizing that no such patients showed no improvement.

DISCUSSION

Thus far, the performance of AVS protocols and cut-offs for defining selectivity and lateralization was examined only in relatively small PA cohorts in single or few centres. We herein examined the performance of widely used SI and LI cut-offs and AVS protocols in identifying lateralised forms of PA in the largest registry of individual AVS studies performed worldwide in major referral centres over a 15 years period of this century. These results extend substantively those of a study that showed disappointingly low rates of surgical cure of hypertension (12%) using centre-defined criteria for interpreting AVA in real-life clinical practice.16
By examining the selectivity rate, on each side and bilaterally, as a function of the SI cut-offs recommended by experts consensus papers,\textsuperscript{14,15} we generated the first important finding: under unstimulated conditions approximately one third of the PA patients would not have gained any diagnostic benefit from being submitted to AVS, because they were judged to be non-bilaterally selective, even with a permissive SI cut-off of 2·0 (Figure 2). With the more restrictive cut-offs endorsed by the 2008 Endocrine Society guidelines,\textsuperscript{19} and still used in many centres,\textsuperscript{15} this worrying proportion was even higher, thus confirming previous data of a smaller pilot study.\textsuperscript{17}

The second important finding regards use of cosyntropin (synthetic ACTH) stimulation, which in the last two decades has become popular, particularly in centres experiencing low rates of bilateral selectivity. Cosyntropin can maximize the step-up of cortisol between the inferior vena cava blood (a surrogate for cortisol concentration in arterial blood) and each adrenal vein blood. Moreover, it minimises stress-induced steroid fluctuations and thereby generation of factitious gradients during sequential (non-simultaneous) AVS. The present results provided unambiguous evidence that when adopting strict cut-offs to define selectivity under cosyntropin stimulation, the rate of bilaterally selective AVS studies was higher than under unstimulated conditions or during metoclopramide stimulation (Supplemental Figures 1, 4). The known secretagogue effect of cosyntropin on cortisol and the selective secretagogue effect on aldosterone of metoclopramide- DA\textsubscript{2} blockade,\textsuperscript{22,23} can explain these findings, which confirmed results from smaller single-centre studies.\textsuperscript{17,23}

Of further importance, the AVIS-2 registry comprised the greatest available collection of AVS studies performed both under unstimulated and during cosyntropin-stimulated conditions in the same patient during the same AVS procedure. Accordingly, it offered a unique opportunity for a paired within-patient and within-AVS comparison of rate of selectivity and lateralisation achieved with the two protocols. Because of these unique
features, this analysis was powered to provide solid information and minimized the untoward effects of potential interindividual confounders.

This comparison revealed a bimodal distribution of SI values post-cosyntropin with a cutting value corresponding to the currently used post-cosyntropin SI cut-off = 5.0 (Figure 3 and Supplemental Figure 2). Thus, even after stimulation and notwithstanding the well-known secretagogue effect of cosyntropin on cortisol augmenting the SI, a subset of patients showed persistently non-selective results, which testifies that cosyntropin stimulation cannot resolve lack of selectivity due to inadequate catheter’s positioning and/or unfavourable adrenal vein anatomy. The latter is not rare, as it was documented in about 15% of the PA patients.\textsuperscript{24,25}

Of further note, by using the post-cosyntropin selectivity as a reference index, we found that the unstimulated SI cut-off that offered the best trade-off of sensitivity and specificity was 1.4 (Fig 3, Suppl. Table 6). This cut-off furnished a rate of bilaterally selective cases similar to that achieved using the post-cosyntropin SI cut-off of 5.0 or 4.0. These findings along with a substantial loss of diagnostically usable AVS studies (Figure 2), represent, in our view, a compelling arguments against use of restrictive cut-offs under unstimulated conditions. The proposal of using less restrictive cut-offs can find support also in the lack of evidence for better outcomes with more restrictive criteria (Figure 5).

The third main finding of the study was that a minority of the PA patients submitted to AVS (from one fifth to a third of the patients, depending on which combination of currently recommended restrictive SI and LI cut-offs) were eventually referred for unilateral adrenalectomy. This low rate is fully consistent with the rate (31.9%) of AVS-guided adrenalectomies seen in the AVIS-2, when the diagnosis was based on the criteria used at each centre.\textsuperscript{16} Overall, the low rates of bilateral success, lateralised studies, and referral for surgery, may even lead to question the usefulness of a test that, besides being costly and invasive, has the ultimate aim of identifying candidates for adrenalectomy. However, by
applying the 40% rate of hypertension cure seen in the subset of patients who received AVS-guided adrenalectomy in AVIS-2 to all those identified with a lateralised form according to less restrictive criteria (Figure 3), we could estimate that the rate of patients cured would double, i.e. increase from 1 every 8 to 1 every 4.

The increased rate of bilateral selectivity warranted by cosyntropin in the majority, albeit not all patients, cannot resolve the disappointingly low diagnostic “yield” of AVS. In fact, there was a price to pay: the lateralisation index fell consistently post-cosyntropin due to a greater decrease of the relative aldosterone secretion index in the culprit than the contralateral side (Table 1). This drop, which was already observed in previous results from smaller studies, translated into judging non-lateralised up to 32% of the PA patients who did show lateralisation under unstimulated conditions. Therefore, these results conclusively disprove the contention that cosyntropin stimulation would increase the sensitivity of AVS for identifying unilateral PA by maximizing the secretion of aldosterone from an APA (or other unilateral forms of PA), i.e. one of the premises for using cosyntropin.

On a final, but substantial, note, these results also revealed a higher rate of adrenalectomies among the patients identified as lateralised PA post-cosyntropin, than under unstimulated conditions. This observation suggests that clinicians posed a higher confidence in post-cosyntropin than in unstimulated AVS results, even though this did not result into higher rates of cure or overall better outcomes (Figure 5).

As discussed elsewhere, some limitations must be acknowledged along with the strengths of the AVIS-2 study. The main comprise its observational design and the lack of predefined criteria to establish bilateral success and lateralisation, which were left to participating centres, both of which were chosen to gather information on use of AVS in real-life clinical practice. These potential limitations were outweighed by several strengths, including a
predefined protocol for data acquisition, and the comprehensive collection of individual hormonal data from the largest multicentre cohort ever studied worldwide.

**Conclusions**

In summary, this study showed that the full diagnostic potential of AVS is currently far from being reached even in major well-experienced referral centres. Moreover, the use of cosyntropin should be carefully weighed by balancing its advantages on ascertaining selectivity with its disadvantages on demonstration of lateralisation. In this decision it is worth considering that limiting the diagnostic yield of AVS to those pinpointed by cosyntropin, who likely entail only the most florid PA phenotypes, did not prove superior to a simpler CT scan-only strategy in an outcome-based randomized trial.

Restrictive cut-offs to determine selectivity and lateralisation resulted into low rates of PA patients appropriately referred for unilateral adrenalectomy; hence, adoption of more tolerant cut-offs and/or use of markers of selectivity that have a higher adrenal-to-peripheral blood step-up than cortisol, such as metanephrines or androstenedione, can be promising strategies to improve the clinical yield of AVS.
CONTRIBUTIONS

GPR designed and directed the study, and supervised the analysis; GR was involved in the development of the Web-based platform for data collection, clarified standing queries with each centre lead investigator after database locking, conceived and performed the statistical analysis; GR and GPR wrote the manuscript. All other authors are lead investigators who collected AVS data in the participating centres, provided critical feedback and helped shaping the study design, protocol, data analysis, research results and manuscript.

DATA SHARING STATEMENT

• Will individual participant data be available: Yes.
• What data in particular will be shared? Individual participant data that underlie the results reported in this article, after removal of date and centre ID that could lead to identification of patient.
• What other documents will be available? Study protocol, statistical analysis code/syntax.
• When will data be available (start and end dates)? Beginning 3 months and ending 36 months following article publication
• With whom? Investigators whose proposed use of the data has been approved by a review committee composed of the lead investigators participating in this study
• For what types of analyses? To achieve aims in the approved proposal.
• By what mechanism will data be made available? Proposals should be directed to gianpaolo.rossi@unipd.it to gain access, data requestors will need to sign a data access agreement.
FIGURE LEGENDS

Figure 1. Study population.

Figure 2. Rate of selectivity at different SI cut-off values. Left panel, empty symbols = unstimulated conditions; right panel, full symbols = cosyntropin-stimulated. Triangles, dotted lines = right and left adrenal veins; circles, continuous lines = bilaterally. * = p < 0·001 for SI_{cosyntropin} = 5·0 vs SI_{unstimulated} = 2·0-5·0.

Figure 3. Impact of cosyntropin on SI and identification of optimal unstimulated SI. Left panels: paired comparison of SI values obtained pre- and post- cosyntropin in 402 AVS with both unstimulated and stimulated data, by side. Medians (interquartile ranges) on top. Black symbols on unstimulated plots represent unstimulated values of post-cosyntropin non-selective cases (below dashed line, SI = 5·0). Right panel: ROC curve for the diagnostic performance of unstimulated SI to predict anatomical, cosyntropin-proved selectivity (SI > 5·0); the optimal cut-off for unstimulated SI (i.e. Youden index) is shown.

Figure 4. Rate of lateralisation and adrenalectomy rate by different diagnostic values. Adrenalectomy/Lateralisation rates according to protocol (unstimulated v.s cosyntropin stimulated), SI cut-off values (1·4, 2·0 and 3·0) and LI cut-off values (2·0-5·0) are shown on top of the bars. Dashed bars = rates of bilateral selectivity, by group, for comparison with lateralisation and adrenalectomy rates.

Figure 5. Blood Pressure Outcomes according to each set of diagnostic criteria. Percentages of cured, improved (marked or mild, for comparability with PASO consensus criteria from Williams TA, Lancet Diabetes Endocrinol 2017; 5(9):689-699; please see also supplemental tab.1), and not improved patients submitted to AVS under unstimulated or cosyntropin-stimulated conditions. Even if their relative proportion is overall similar across criteria, the absolute rates of cured and markedly improved patients out of all those submitted to AVS decreases progressively with use of more restrictive cut-offs.
REFERENCES


1820 patients
1625 individual AVS data
Exclusion of cases performed before 2000 (n=195)

1274 AVS
742 AVS (45.8%)
Unstimulated

742 AVS (45.8%)
Cosyntropin-stimulated

402 AVS
(24.7%)
Metoclopramide stimulated AVS

123 AVS
(7.5%)
Stimulated AVS

637 AVS
1004 AVS
Cases with available therapeutic outcome data

1625 individual AVS data

1820 patients
FIG. 2

Unstimulated Cosyntropin

Bilateral
Left side
Right side

Selectivity (%)

38.4
44.7
52.4
67.3
86.3
90.2
82.9
84.1
85.7
87.1
81.3

Cosyntropin

Unstimulated
Selectivity index (SI)

Unstimulated SI

Right side SI

Left side SI

AUC 0.756

p < 0.001

Spec: 62%
Sens: 92%

1.40

0 20 40 60 80 100

Specificity

0 20 40 60 80 100

Sensitivity

(2.0·95-53·09)
(1.69-10·24)
(3·09-17·20)
(22·84-48·42)
(23·84-48·42)
(4·24-11·48)
Adrenalectomy rate (%) / Lateralization rate (%)
Table 1: Paired comparison of relative aldosterone secretion index (RASI) by side and lateralization index (LI) between unstimulated and post-cosyntropin conditions. Data presented as median (interquartile range). *SI = 2·0 was used for definition of unstimulated LI; SI = 5·0 was used for definition of post-cosyntropin LI. LI was performed at different SI cutoff values (not shown). Wilcoxon test; significance set at p < 0·05.

<table>
<thead>
<tr>
<th></th>
<th>Whole cohort</th>
<th>Unilateral PA</th>
<th>Non-dominant side</th>
<th>Dominant side</th>
<th>RASI (%)</th>
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<td><strong>LI</strong></td>
<td>1·8</td>
<td>1·3-2·0</td>
<td>0·47-2·34</td>
<td>0·01</td>
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<td><strong>Δ RASI (%)</strong></td>
<td>-42·0</td>
<td>-9·3-6·2</td>
<td>1·25</td>
<td>7·26</td>
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<tr>
<td><strong>p</strong></td>
<td>&lt; 0·001</td>
<td>&lt; 0·05</td>
<td>0·020</td>
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Paired comparison in the subcohort of patients with bilaterally selective AVS on both unstimulated and post-cosyntropin conditions.
Table 2: Diagnostic discrepancy between paired unstimulated and cosyntropin-stimulated AVS results

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<tr>
<th></th>
<th>CI (95%)</th>
<th>SI &gt; 0</th>
<th>LI &gt; 0.5</th>
<th>Lat</th>
<th>Bilat</th>
<th>McNemar</th>
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**Cosyntropin-stimulated**

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Paired diagnostic comparison in the subcohort of patients with bilaterally selective AVS on both unstimulated and post cosyntropin conditions. Data presented as n (%) according to use of different diagnostic criteria. Lat = AVS results suggesting lateralization according to corresponding diagnostic cut-off values; Bilat = AVS results according to use of different diagnostic criteria. LI > X results suggest bilateral PA according to corresponding diagnostic cut-off values. Baseline LI cutoff = 4.0 was not compared with post cosyntropin LI cutoff = 3.0 because there is no published evidence of any center using a more stringent approach under unstimulated conditions. McNemar test; significance set at p < 0.05.
Subtyping of Primary Aldosteronism in the AVIS-2 Study:
Assessment of Selectivity and Lateralization

RESEARCH INTO CONTEXT

Evidence before this study
Patients with unilateral primary aldosteronism (PA), the most common curable form of arterial hypertension can benefit from unilateral laparoscopic adrenalectomy, while those with bilateral PA require life-long medical treatment. To discriminate between unilateral and bilateral PA, the guidelines recommend adrenal vein sampling (AVS).

However, real-life data from the Adrenal Vein Sampling International Study (AVIS)-2 showed that the proportion of patients who ultimately benefitted from AVS-guided adrenalectomy was remarkably low, mainly because of the criteria used to define selectivity (i.e. adequate adrenal blood sampling) and lateralisation, which were heterogeneous across centres. The performance of different criteria and/or protocols, i.e. use of cosyntropin-stimulation or not, has been examined only in relatively small studies involving a single or few centres thus far. Hence, recommendations on how to optimally perform and interpret AVS remain vague or even disagree.

Added value of this study
This study examined in detail the performance of widely used AVS selectivity and lateralisation criteria and protocols in identifying lateralised forms of PA in AVIS-2, the largest international prospective registry of individual AVS studies performed over 15 years in major referral centres. Moreover, it included the greatest available paired within-patient within-AVS comparison of studies performed under unstimulated and cosyntropin-stimulated conditions.

Results showed that use of currently recommended strict criteria resulted into less than 25% of PA patients ultimately referred for unilateral adrenalectomy, a rate that was not compensated by outcome benefits compared to lower diagnostic cut-offs. Use of cosyntropin, while increasing selectivity, decreased significantly the lateralisation rates and did not provide better outcomes.

Implications of all the available evidence
AVS is currently far from being exploited to its full diagnostic potential. Hence, the ethical justification of using such costly and invasive test, which has the ultimate aim of identifying candidates for adrenalectomy, might be questioned. Criteria and protocols better than those currently in use need to be exploited.