Title: The Clinical Outcomes of 1625 Patients with Primary Aldosteronism Subtyped With Adrenal Vein Sampling

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Abstract

Background. We sought to measure the clinical benefits of adrenal venous sampling (AVS), a test recommended by guidelines for primary aldosteronism (PA) patients seeking surgical cure, in a large registry of PA patients submitted to AVS.

Methods. Data of 1625 consecutive patients submitted to AVS in 19 tertiary referral centers located in Asia, Australia, Europe and North America were collected in a large multi-center international registry. The primary endpoints were the rate of bilateral success, ascertained lateralization of PA, adrenalectomy, and of cured arterial hypertension among AVS-guided and non AVS-guided adrenalectomy patients.

Results. AVS was successful in 80.1% of all cases and allowed identification of unilateral PA in only 45.5% by the criteria in use at each center. Adrenalectomy was performed in 41.8% of all patients and cured arterial hypertension in 19.6% of the patients, two-fold more frequently in women than men ($p<0.001$). When AVS-guided, surgery provided a higher rate of cure of hypertension than when non-AVS-guided (40.0 vs 30.5%, $p=0.027$). Compared to surgical cases, patients treated medically needed more antihypertensive medications ($p<0.001$) and exhibited a higher rate of persistent hypokalemia requiring potassium supplementation (4.9% vs 2.3%; $p<0.01$) .

Conclusions. The low rate of adrenalectomy and cure of hypertension in PA patients seeking surgical cure indicates suboptimal AVS use, possibly related to issues in patient selection, technical success, and AVS data interpretation. Given the better outcomes of AVS-guided adrenalectomy, these results call for actions to improve the diagnostic use of this test that is necessary for detection of surgical PA candidates.

INTRODUCTION

Despite a high reported prevalence,[1–4] primary aldosteronism (PA) is under-diagnosed in actual practice, mainly because it is erroneously believed to be rare, and because the classical clue of hypokalemia is only found in a minority of patients with PA when systematic screening is employed.[1] The under-detection of PA has serious consequences: a large number of patients with PA remain exposed to long-term aldosterone excess and thus develop frequent target organ damage and cardio-vascular events, such as atrial fibrillation, stroke, myocardial infarction, and heart failure.[5,6] Targeted treatment of PA following timely diagnosis can prevent these adverse events, improve quality of life, [6–8] and provide long-term cure with reversal of cardiovascular damage.[9] Therefore, efforts aimed at increasing the frequency of accurately diagnosed PA are worthwhile, in line with current expert recommendations.[10]

Subtyping of PA is key for selecting the most appropriate targeted treatment, either adrenalectomy when a unilateral adrenal form (mainly aldosterone-producing adenoma and unilateral hyperplasia) is ascertained, or life-long medical treatment with mineralocorticoid receptor antagonists (MRA) in bilateral adrenal forms (predominantly bilateral adrenal hyperplasia). Recognizing that alternative subtyping methods (such as imaging and biochemical tests), and functional imaging (NP59 scintigraphy and PET-metomidate) are either inaccurate or rarely available, guidelines advocate use of adrenal vein sampling (AVS),[11] a procedure introduced in 1957,[12] and thereafter widely applied with documented success.[13,14] Despite the low risk of adrenal vein rupture in experienced hands,[15,16] AVS remains technically challenging, as shown by the 70% rate of unsuccessful studies in a nationwide survey in Germany.[17] Even the interpretation of bilaterally successful AVS is by no means straightforward, and criteria to define correct catheterization and lateralization of aldosteronism remain quite variable across centers, as shown by the Adrenal Vein sampling International Study 1 (AVIS-1).[15,18] Moreover, robust evidence of clinical benefit with AVS is lacking, and thus the quality of evidence for guideline recommendations is at most moderate.[11]

Accordingly, many patients with PA still undergo surgery without prior demonstration of lateralized aldosterone excess, a practice potentially leading to unnecessary adrenalectomy, and/or to removal of the wrong adrenal in up to a third of cases.[19]

To better understand and optimize AVS usage, the AVIS-2 study created a large international registry of individual AVS data. We herein report on the main results of this study, i.e. clinical benefits for the AVIS-2 patients in terms of success rate, ascertained lateralized aldosterone secretion leading to unilateral adrenalectomy, correction of aldosteronism, rate of cure/improvement of arterial hypertension, and changes of antihypertensive drug treatment needed to achieve control of BP values.

METHODS

The authors declare that all supporting data are available within the article [and its online supplementary files]. The original protocol of AVIS-2, which started in 2012 as an observational multi-center study of individual consecutive AVS studies performed worldwide, was registered at clinicaltrials.gov (NCT01234220); it was thereafter amended to allow for inclusion of additional variables and centers to reach the target recruitment number of 1500 patients with PA submitted to AVS.

Centre selection criteria

The methods and criteria used to identify eligible centers are briefly recapitulated here, but are reported in detail as supplemental material. The participating centers were selected based on participation in the AVIS-1 study and/or publications on AVS, as identified through a PubMed search. All procedures were carried out according to the Helsinki Declaration. The protocol of the study was approved by the Ethics Committee of both coordinating and participating centers.

Inclusion/exclusion criteria

After identification of the eligible centers the inclusion criteria were: a) age ≥ 18 years; b) agreement to participate in the data collection; c) approval of the local ethics committee. The only exclusion

criteria were unwillingness of the lead investigator to participate and/or lack of local ethical/institutional approval.

Data collection and harmonization

Data was systematically anonymized to permit privacy protection in an *ad hoc* web-based platform using a pre-defined form for on-line data collection (reported in the Supplemental Material) with appropriate filters to prevent input of values that were not biologically plausible and/or associated with incorrect units of measure. This ensured high quality of the data, which were securely stored in a protected server at the coordinating center. A summary list of collected variables is reported in the Supplemental Material. The PI had full access to the dataset; each local lead investigator had access with username and password to his/her center's database.

Definitions

The biochemical definitions for selectivity index (SI), lateralization index (LI), and adrenal vein rupture definitions (summarized in the Supplemental Table 1) were in line with those commonly used.[18] The BP outcome following intervention (Supplemental Table 2) used a pre-defined protocol to group patients into categories denoted as *cure*, *marked*, *mild*, and *no improvement*. Post-intervention biochemical failure (i.e. non-resolution of aldosterone excess) was defined as persistence of hypokalemia and/or of an aldosterone-to-renin ratio > 30 (ng/dl)/(ng/mL/h) with persistently suppressed plasma renin activity (< 1 ng/mL/h), which is associated with higher risk of incident cardiometabolic events and death.[6]

Data handling and statistical analysis

After database locking, data were checked for internal consistency and queries were clarified with each center's lead investigator. Biochemical data were then harmonized to a standard measurement unit before undertaking the statistical analysis. Results are expressed as mean ± SD, or median and interquartile range (IQR), as appropriate. Continuous variables were tested for normal distribution

and log-transformed if they showed a skewed distribution before statistical comparisons with parametric tests. Nonparametric tests were used if a gaussian distribution could not be achieved. Pearson's χ^2 test was used to analyze categorical variables and proportions. Statistical significance was set at $p<0.05$. SPSS (vers. 25 for Mac, IBM-SPSS Bologna, Italy), and Prism (vers. 8.02 for Mac, GraphPad Software, La Jolla California USA) softwares were used for the analysis.

RESULTS

Baseline characteristics of the population

Four continents (Europe, including Russia, Asia, North America, and Australia) contributed to AVIS-2 with a total of 19 centers; upon database locking, 1820 individual AVS datasets were available. To maintain a homogeneous cohort reflecting modern practice, it was decided to limit the analysis to studies performed between 2000 to 2015, which left a total of 1625 individual AVS studies (Figure 1) for analysis. The majority (76.5%) of the patients were recruited in Europe; Caucasians (75.2%) predominated over Asian (20.7%), African and African-American (3.6%) and Hispanic (0.6%) participants.

The main features of the population are shown in Table 1; number of AVS performed, technique, protocol and diagnostic criteria in use at participating centers are in Supplemental Table 3. Briefly, there was a preponderance of men (61%), with an average age of 50.8 ± 10.8 years and BMI of 28.4 ± 5.3 Kg/m^2; overweight and obesity, which was more commonly found in men than women (X^2 = 118.2, $p<0.001$), was present in 37.2%. Only 41.4% of the patients had hypokalemia; plasma aldosterone concentration (PAC), plasma renin activity (PRA), and the aldosterone/renin ratio (ARR) values were those expected for a population of patients with PA. Heterogeneity of the recruited cohorts across centers was evident in that the biochemical phenotype was more pronounced in some centers and milder in others, likely reflecting different screening strategies, with baseline differences (X^2 = 160.0, $p<0.001$) in the rate of hypokalemia and of concomitant pharmacological treatment during biochemical measurements (X^2 = 1037.4, $p< 0.0001$).

Information on ongoing treatment was available in 91% of the cases: 42.3% had an adequate wash-out, but 48.7% were tested while using potentially interfering medications. While the lack of adequate wash-out had an impact on the assessment of lateralization, it did not translate into significant differences of BP outcome.

CT and/or MR imaging data were available at AVS in 90.5% of the whole population. Adrenal nodules were more commonly seen on the left than the right side (40.8% vs 20.7% $p<0.001$) and in women than men ($p<0.0001$). Bilateral adrenal nodules were reported in 8.4%; no adrenal nodules were reported for 30.1% of all cases.

Given the long recruitment period, we could observe that the number of AVS studies increased after 2009 (Supplemental Figure 1), i.e. after the publication of the 2008 guidelines,[20] and that there was a gradual shift toward less florid clinical phenotypes submitted to AVS, as revealed by lower BP ($p < 0.001$) and PAC values ($p = 0.027$), and a trend toward higher serum K^+ ($p = 0.097$).

AVS performance and results

The overall rate of adrenal vein rupture was 0.7% with no between-sex differences (Supplemental Figure 2); all cases resolved with clinical surveillance and pain-killer medications, e.g. only with conservative treatment.

The centers were almost equally divided between the bilateral simultaneous and the sequential technique for AVS (46.6% and 53.4%, respectively, Supplemental Table 3). By each center's criteria, bilateral selectivity (catheterization success) was attained in 80.1% of the studies, slightly more commonly in men than in women (Figure 2, upper panels). Thus, one fifth of the studies could not be used for diagnostic subtyping. The sequential sampling technique was associated with a lower rate of bilaterally selective studies (76.2% vs 84.7%, $X^2 = 18.4$, $p< 0.001$).

By each centers' biochemical definition used to determine lateralization (Supplemental Table 3), a unilateral PA subtype was identified in 45.5% of all cases with no between-sex (Figure 2, bottom panels) or across-ethnicities differences. Thus, AVS results, as locally interpreted, did not support an

indication for unilateral adrenalectomy in 54.5% of all cases, because of lack of bilateral selectivity (19.9%) and/or of lateralization (34.6%) (Figure 1).

Primary endpoints

Rate of adrenalectomy and medical treatment

Information on treatment modality was available in 1329 patients, i.e. 81.8% of the entire cohort (Figure 1 and Supplemental Figure 3). Adrenalectomy was performed in 679 patients (41.8% of the entire cohort); involving the left more often than the right side (59.9% and 39.9%, respectively). Bilateral adrenalectomy was performed in only 0.1%. Surgery was AVS-guided in only 76.4% (n= 519; 31.9% of the entire cohort), however 17.2% of the patients with PA that showed lateralization, (i.e. 6.6% of the entire cohort), still did not receive surgery; conversely, 23.6% of adrenalectomies were not AVS-guided (n= 160; 9.9% of the entire cohort). Hence, treatment was AVS-guided in 1061 (i.e. 519 adrenalectomized + 542 medically-treated), corresponding to 79.8% of the 1329 patients for which information on treatment was available and 65.3% of the entire cohort (Figure 1).

The AVS-guided and non-AVS-guided adrenalectomized patients did not differ in baseline features (Supplemental Table 4), but the latter showed a trend toward a higher rate of single visualized adrenal masses at imaging; 78% of them had non-bilaterally selective (non-successful) AVS and only 22% did not reach center-specific criteria for lateralization, suggesting that the majority of the surgical decisions were made based on other criteria, including contralateral suppression, pointing towards unilateral disease despite failed AVS. Very few patients went to surgery despite successful, non-lateralizing AVS results.

Pharmacological therapy was the long-term treatment modality in 650 patients, i.e. 40% of the whole cohort (Figure 1 Supplemental Table 3). The rate of assignment to medical or surgical treatment showed no between-sex differences (X^2 = 2.77, p=0.43; Supplemental Figure 3), but evident ethnicity-related disparities, as more adrenalectomies were undertaken in Caucasians than in the other ethnicities (X^2 = 50.5, p<0.001).

Final diagnosis and patient-specific outcomes

Information on post-intervention BP and biochemical measures at follow-up were available in 75.3% and 47.2%, respectively (Supplemental Figure 4). Analysis of the BP outcome showed that cure of hypertension was accomplished in 19.6% of all patients: the proportion of cases that showed *cure* was overwhelmingly better in the surgically than in the medically treated group (37.8% vs none, $p<0.001$; Figure 3, Panel A), while that of *marked or mild improvement* did not differ, likely reflecting an intensified drug treatment in the medically treated group, as detailed in the next section; moreover, the rate of not improved was 5-fold higher in the medically treated than in the surgically treated group (22.2% vs 5.3%, $p<0.001$).

The rate of cure was significantly higher in women than in men (Figure 3, panels C and D), both when adrenalectomy was AVS-guided (58% in women vs 28.% in men, $p< 10^{-4}$, panel C), but also when it was non-AVS-guided (47.8% and 16.7%, respectively; $p< 10^{-3}$; Figure 3, panel D). Moreover, the rate of *non-improvement* was two-fold higher in men than in women.

Pharmacological treatment

Starting from a similar mean medication burden at baseline (Figure 4, panel A), in the adrenalectomized patients the number of drugs required to control BP at follow-up was less than half than in the medically treated patients (1.16 (95% CI: 1.06-1.26,) vs 2.60 (2.48-2.70), $p<0.001$) (Figure 4, panel B). When surgically treated patients were split into those who received AVS-guided adrenalectomy and those where surgery was non AVS-guided, fewer medications were required to achieve control of high blood pressure in the former than in the latter patients (Figure 5).

Biochemical outcome

Full biochemical follow-up data was more often available in adrenalectomized than in medically treated patients (31.3% vs 15.9%, $X^2 = 360.7$, $p < 0.001$), in Caucasians (57.2%) and Asians (51.4%) than in Africans and African-Americans (20.5%) or in Hispanics (42.9%) ($X^2 = 24.6$, $p < 0.001$).

Out of 1141 patients with available serum K^+ follow-up data, 96.4% were normokalemic, with slightly higher rate in the surgically versus medically treated group (98% and 95%, respectively; $X^2 = 7.1$, $p = 0.009$). Accordingly, the need for K supplementation was lower in the surgically than in the medically treated group (2.3% vs 5.6%, $X^2 = 8.203$, $p = 0.004$).

Among the 604 patients with ARR data at follow-up, the values were lower following adrenalectomy than while on medical therapy (5.2 (2.1-10.5) vs 24.8 (11.2-55.9), $p < 0.001$), but remained elevated (with suppressed renin) in 6.5% of adrenalectomized patients (6.2% and 7.4% of AVS-guided and non-AVS-guided cases, respectively; p = ns) and in 24.4% of the medically treated patients ($X^2 = 35.0$, $p < 0.001$).

Sensitivity analysis

To determine if a disproportionate recruitment across centers could have biased these results, we performed a sensitivity analysis for all end-points by inclusion/exclusion of centers into those that enrolled more or less than 100 patients (Supplemental Table 4). This showed that the main outcome end-points, i.e. rate of bilateral selectivity and lateralization at AVS, BP cure and biochemical success, were similar between groups, which made unlikely a center-related recruitment bias.

DISCUSSION

The creation of the largest registry of individual AVS studies performed in major referral centers over a 15 years period provided a unique opportunity to examine the real-life benefits of AVS worldwide. This practice survey is quite important at a time when guidelines[10,11,20] and experts[14] recommend AVS for PA subtyping, while single-center findings,[21] a randomized comparison of CT with AVS,[22] a large retrospective study,[23] and a histopathology study of CT-negative adrenalectomized patients with PA,[24] collectively would challenge the advisability of this

recommendation.

With the strength of the largest comparison of various PA treatments thus far, AVIS-2 demonstrated the clear superiority of adrenalectomy over medical therapy in terms of blood pressure benefits (Figure 3), pharmacological burden (Figure 3), and also measured biomarkers of post-intervention success. The recent demonstration that medically-treated patients with PA, who are incompletely relieved of exposure to aldosterone excess, remain at higher risk of cardiovascular events and death,[6–8] emphasizes the relevance of these findings. Importantly, AVIS-2 also showed that in the wide population of patients seeking surgical cure, functional subtyping of PA by AVS was associated with a higher rate of hypertension cure (Figure 3), a lower number of medications required to control persistently high BP values (Figure 4), and a tendency for better biochemical benefits than non AVS-guided adrenalectomy.

Based on experts' opinion, standardized (PASO) criteria to classify outcomes were recently proposed and retrospectively applied to a cohort of AVS-guided adrenalectomized patients with PA.[25] They were thereafter used to compare AVS with CT-imaging in another cohort undergoing adrenalectomy.[23] AVIS-2 outcome definitions were defined prior to PASO publication, but are remarkably comparable to the PASO definitions (Supplemental Table 2) and led to similar estimates of clinical benefits. A notable exception to this was the higher rate of cure of hypertension in the AVS-guided adrenalectomy cohort, which highlights the importance of AVS-based decision making. Unlike a PASO sub-study of patients selected post-adrenalectomy, which was restricted by protocol to those with clinical and biochemical follow-up,[23] AVIS-2 comprised a large and more generalized cohort of both medically- and surgically-treated patients studied in this century, reflecting global PA care in real life during that time.

Interestingly, only about four out of ten patients with PA were eventually referred for adrenalectomy in AVIS-2 (Figure 1), and an even smaller proportion (19.6%) were cured from hypertension, so that overall, only 1 in 8 (12.1%; 197/1625) patients benefited from AVS-guided cure in terms of blood

pressure outcome.

These low rates may be explained by several reasons, primarily by poor performance or interpretation of AVS. Firstly, using the preferred biochemical interpretation criteria at different centers, and irrespective of AVS being performed after pharmacological (cosyntropin) stimulation, bilateral adrenal vein selectivity, an essential prerequisite for diagnostic use of AVS, failed in about one fifth of all studies. The success rate was significantly higher in centers that used the bilaterally simultaneous AVS technique, but unfortunately the different protocols/interpretative criteria across centers, precluded determination of whether this was due to effects of stress and pulsatile hormone secretion (affecting the assessment of both selectivity and lateralization in the sequential approach,[26]), or to center-specific expertise.

Secondly, according to the biochemical definitions of unilateral disease used at the different centers, a lateralized subtype of PA could be identified in less than half of all cases (Figure 1): in the remaining patients the AVS results did not support unilateral adrenalectomy, either because of failure of catheterization in about one fifth of the cases, and/or of demonstration of lateralization in about one third. Likely because of severe/resistant hypertension, AVS was necessarily performed without adequate wash-out of interfering medications[18] in about 49% of patients, which could partly explain failure to show lateralization. Nonetheless, with the caveat associated with the low statistical power, the BP outcome of patients submitted to AVS with and without wash-out did not show significant differences, suggesting that the work-up of the PA patients might be simplified.

With present patterns of AVS use, the low rate of diagnostic lateralization leading to curative surgery appears paradoxically to be of low overall value for a test that is invasive, expensive, and not completely free of risk.[15]

On the other hand, our results suggest that of the people who undergo AVS, 45.5% will have diagnostic AVS studies showing lateralization, all of whom should proceed to surgery. Laparoscopic adrenalectomy generates good responses, i.e. cure or marked improvement in BP in ~90% of women,

and ~75% of men. Hence, using these numbers, ~32% of women (1 out of 3 women) who undergo AVS and ~27% of men (1 out of 4 men) who undergo AVS will show cure or marked BP benefit from AVS-guided surgical treatment of PA.

Other remarkable findings were that: i) in a PA cohort seeking surgical cure, adrenalectomy was AVS-guided in only 31.9% of the entire cohort, i.e. about three quarters of those who underwent surgery; ii) a non-negligible rate (9.9%) of all patients, had surgery without AVS-based proof of lateralization. Clinically these two groups were similar, aside from a 78% rate of AVS failure in the group that had surgery without AVS-based proof of lateralization. Non AVS-guided adrenalectomy and the decision to avoid surgery despite successful AVS showing lateralization (6.6%), suggest that either the clinicians did not trust the AVS results, and/or imaging results were more valued than AVS. The possibility that in some cases adrenalectomy was based on the presence of AVS-biochemically determined contralateral adrenal aldosterone suppression cannot be ruled out, although the accuracy of this index for identification of unilateral PA[27] remains to be conclusively demonstrated.[11]

With regard to adrenal imaging, it is worth emphasizing that a sizable proportion of patients showed no adrenal nodules or bilateral nodules (30.1% and 8.4%, respectively), thus offering no useful diagnostic information as to the PA subtype.

On the whole, and despite the clearcut benefit of surgery for PA benefits, these findings raise questions regarding the clinical usefulness of AVS, as currently performed and interpreted, and also the appropriateness of currently used biochemical definitions of bilateral selectivity and unilateral aldosteronism, which will be addressed in depth in another paper.

Finally, we would also like to note the shift toward a less florid clinical phenotype of patients with PA submitted to AVS over the years, which expands and re-enforces the perceived necessity of this test. Moreover, our results document for the first time a clear-cut sex dimorphism in patients with PA undergoing AVS: i) women were less likely than men to have bilaterally successful AVS (Figure 2),

raising questions about anatomical differences; ii) they were more likely to obtain cure of hypertension with surgery particularly when adrenalectomy was AVS-guided, in line with what was suggested in a retrospective survey.[25]

Limitations and strengths

The lack of follow-up data, particularly on biochemical cure, in a proportion of the patients with PA in this study is both a limitation of AVIS-2, because it can be of concern for confirming the diagnosis of lateralized PA in adrenalectomized patients.[1,28] However, it shows that this study is a real-life snapshot of current clinical practice, in that it did not introduce a selection bias by excluding the patients without follow-up data. Notably, completeness of follow-up data was a function of patient ethnicity, suggesting that it involved factors related to local health care organization: while follow up data did not differ by treatment modality, scrutiny of the missing data elements showed that it may be explained by cases where patients were seen at tertiary centers only for AVS, after which they were sent back to their referring hospital, where follow-up data on were not systematically gathered. Another reason could be that clinicians (especially in earlier years of the study) assessed mainly BP, rather than repeat ARR as the main indicator of surgical outcome. Given the prognostic value of persistently suppressed renin,[6] initiatives such as PASO-based systematic, standardized biochemical re-assessment at follow-up,[25] are important. Other possible limitations of AVIS-2 are related to its observational design, which relied upon local investigators' interpretation of AVS to establish bilateral success and lateralization. As mentioned above, this was deliberately chosen at the outset to gather real-life information on AVS use in clinical practice. It might also be argued that, in the absence of a pre-defined medical treatment protocol, evaluation of pharmacotherapy benefits has inherent limitations; however, it has recently pointed out that other approaches, like use of defined daily doses, are similarly far from perfect.[29] Moreover, the pre-defined categories of blood pressure outcome definitions in AVIS-2 minimized arbitrary comparisons to the surgery group.

CONCLUSIONS

Notwithstanding the high prevalence of PA and the crucial place of AVS for selecting treatment, AVIS-2 showed that the current clinical use of AVS has not been entirely successful in leading to high-value benefits for a substantial proportion of the patients who undergo such test. While the key role of AVS is clearly supported by the markedly higher rate of cure when adrenalectomy was AVS-guided. with the criteria currently in use at referral centers to establish the success of catheterization and ascertain lateralization, only a minority of the patients with PA seeking surgical cure were referred for adrenalectomy and ultimately cured based on AVS results.

As the picture could be even more disappointing outside of the highly-experienced referral centers participating in AVIS-2, these findings represent a strong call for actions aimed at improving the global clinical use of this essential procedure, with the ultimate goal to increase the number and proportion of patients with PA who are successfully detected for clinical and biochemical cure through adrenalectomy.

PERSPECTIVES

Several actions are being taken to improve the clinical use of AVS; one such actions is the on-going Intra-Procedural Cortisol Assay During Adrenal Vein Sampling (I-PADUA, registered at ClinicalTrials.gov number, NCT03449797) a randomized study aimed at testing the hypothesis that use of a rapid semiquantitative assay performed during AVS can improve the achievement of bilateral selectivity, and thus the success of this technically demanding procedure.[30]

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Novelty and Significance

What Is New

- AVIS-2, the largest multi-center international registry of patients seeking surgical cure of primary aldosteronism (PA), showed the clear-cut superiority of AVS-guided adrenalectomy over medical therapy in terms of blood pressure benefits and reduced pharmacological burden.
- It also demonstrated the suboptimal clinical usefulness of adrenal vein sampling (AVS), as currently performed and interpreted.
- **What Is Relevant?**
- AVS was successful in 80.1% of all cases and allowed identification of unilateral PA in only 45.5% by the criteria in use at each center. Adrenalectomy was performed in 41.8% of all patients and cured arterial hypertension in 19.6% of the patients, two-fold more frequently in women than men ($p<0.001$).
- When AVS-guided, surgery provided a higher rate of cure of hypertension than when non-AVS-guided and a lower need for antihypertensive agents at follow-up.

Summary

- Given the better outcomes of AVS-guided adrenalectomy, these results call for actions to improve the diagnostic use of this test that is necessary for detection of surgical PA candidates.

CONTRIBUTIONS

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

FIGURE LEGENDS

Figure 1. Flow chart of the AVIS-2 Study. The percentages were calculated using the total number (n=1625) as denominator. See text for explanations.

Figure 2. Rate of bilateral selectivity and lateralization diagnosis at AVS by sex. Upper panels: rate of successful (bilaterally selective) AVS according to the criteria used in the different centers in the whole cohort (pie graph) and divided by sex (bar graph). Please note the higher success rate of AVS in men than in women. Lower panels: rate of the AVS studies showing lateralized PA according to the criteria adopted in the different centers in the whole cohort (pie graph) and divided by sex (bar graph). Lack of lateralization by these criteria was seen in over half the cases, while the rate of lateralized studies was similar in both sexes (bottom panels).

Figure 3. Blood Pressure Outcomes. The BP outcome was (Chi-Square = 335.5, $p < 10^{-4}$) better in the adrenalectomised than in the non-adrenalectomised, medically-treated patients (Panel A), among which none was cured. The patients submitted to AVS-guided adrenalectomy (non shaded bars) showed a higher ($p = 0.02$) rate of cure than those in whom surgery was not AVS-guided (shaded bars) (Panel B). Overall among adrenalectomized patients, both when surgery was AVS-guided (Panel C, Chi-Square = 41.2, $p < 10^{-4}$)) and when it was non AVS-guided (Panel D, Chi-Square = 38.6, $p< 10^{-3}$) women showed a markedly higher rate of cure and a lower rate of non improvement than men.

Figure 4. Pharmacological treatment. Number of antihypertensive drugs that were necessary to achieve control of high BP values in the patients assigned to adrenalectomy or medical treatment at baseline (Panel A) and at follow after target treatment (Panel B). Please note how adrenalectomy was associated with a highly significant reduction (shift to the left of the distribution) of the number of antihypertensive drugs, as compared to the medically treated group.

Figure 5. Pharmacological treatment in adrenalectomized patients. Number of antihypertensive drugs that were necessary to achieve control of high BP values in the patients submitted to AVS-

guided and non AVS-guided adrenalectomy. Please note the higher rate of cure, i.e. proportion of patients requiring no drugs, and the lower proportion of patients requiring more than 5 drugs in the former than in the latter group.

Table 1: Baseline demographic, clinical and biochemical features of the 1625 patients with PA who were submitted to adrenal vein sampling.

Variable	*Value*
Age (years)	*50.8 ± 10.8*
Sex (M/F), n (%)	*985 (60.6)/ 640 (39.4)*
Ethnicity (%)	
Caucasians	*75.2*
Asians	*20.7*
Africans	*3.6*
Hispanics	*0.6*
Body Mass Index (Kg/m^2)	*28.4 ± 5.3*
Systolic BP (mmHg)	*152 ± 20*
Diastolic BP (mmHg)	*92 ± 13*
Heart rate (beats/min)	*73 ± 12*
Anti-hypertensive treatment (n. of drugs)	*2.26 (0-8)*
Serum K^+ (mmol/L)	*3.6 ± 0.5*
Hypokalemia (%)	*41.4*
PRA (ng/mL/h)	*0.30 (0.20 – 0.57)*
PAC (ng/dL)	*24.8 (15.4 – 33.6)*
PAC (pmol/L, Système International)	*688 (428 - 933)*
ARR (ng/dL)/(ng/mL/h)	*65.5 (36.3 – 118.8)*
ARR (pmol/L/ng/mL/h, Système International)	*1818 (1008 - 3298)*
Imaging (Single node/bilateral nodes/normal adrenals, %; n = 1470)	*61.5/8.4/30.1*

Mean±SD, or median and IQ range (PRA, PAC and ARR) or mean and range (n. of drugs). Abbreviations: PRA: plasma renin activity; PAC: plasma aldosterone concentration; ARR: aldosterone/renin ratio.

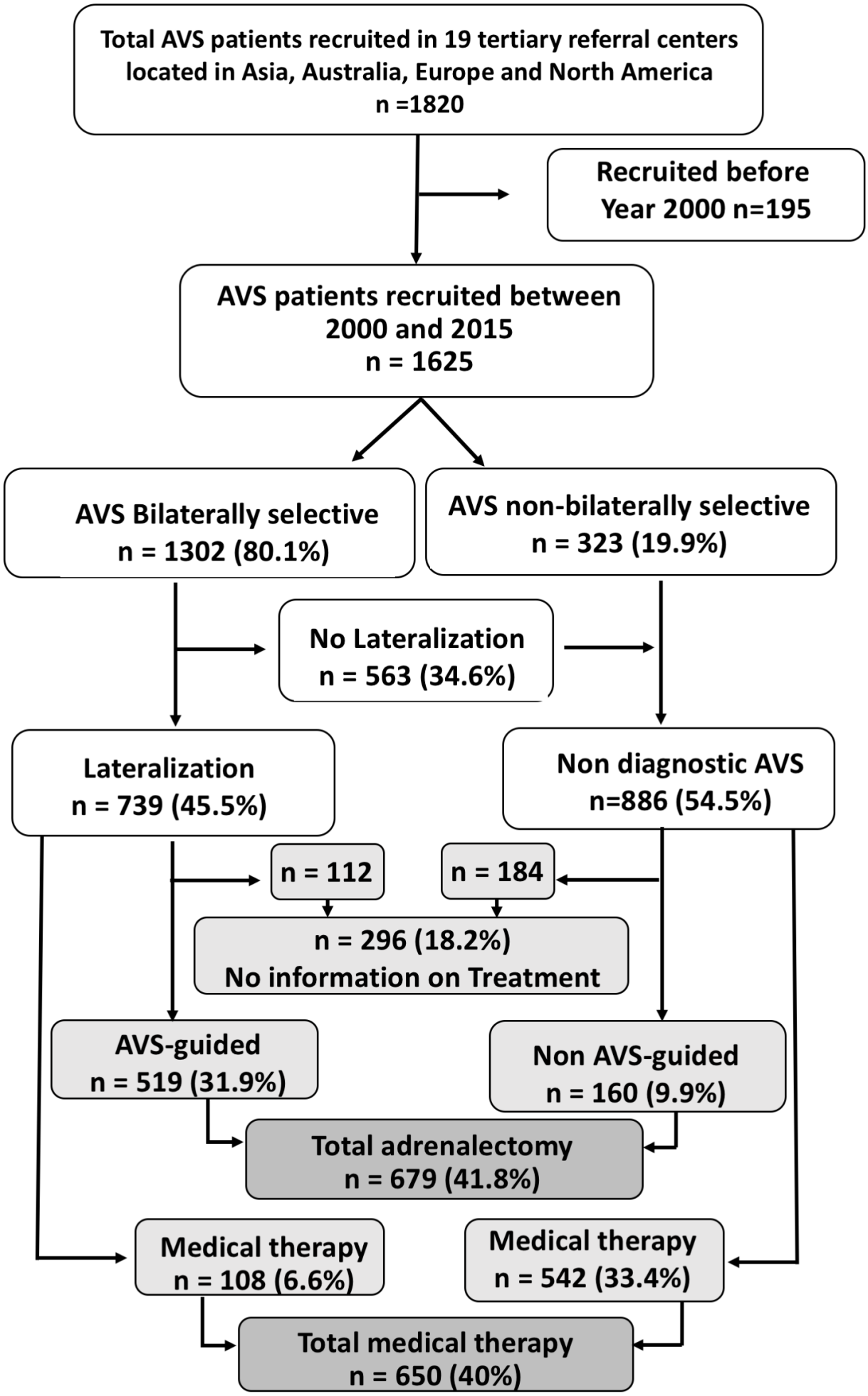
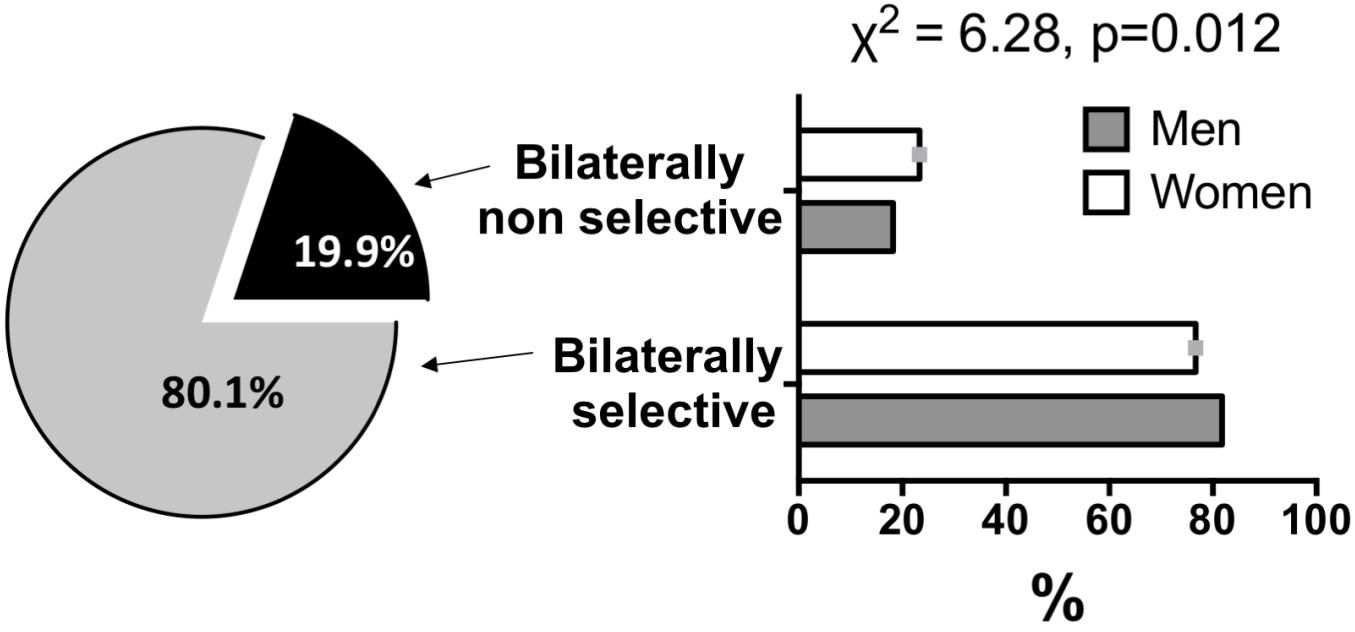

Total AVS patients recruited in 19 tertiary referral centers located in Asia, Australia, Europe and North America
n =1820
Recruited before Year 2000 n=195
AVS patients recruited between 2000 and 2015
n = 1625
AVS Bilaterally selective
n = 1302 (80.1%)
AVS non-bilaterally selective
n = 323 (19.9%)
No Lateralization
n = 563 (34.6%)
Lateralization
n = 739 (45.5%)
Non diagnostic AVS
n=886 (54.5%)
n = 112
n = 184
n = 296 (18.2%)
No information on Treatment
AVS-guided
n = 519 (31.9%)
Non AVS-guided
n = 160 (9.9%)
Total adrenalectomy
n = 679 (41.8%)
Medical therapy
n = 108 (6.6%)
Medical therapy
n = 542 (33.4%)
Total medical therapy
n = 650 (40%)

Figure 1


χ2 = 6.28, p=0.012
19.9%
80.1%
Bilaterally non selective
Bilaterally selective
Men
Women
0
20
40
60
80
100
%

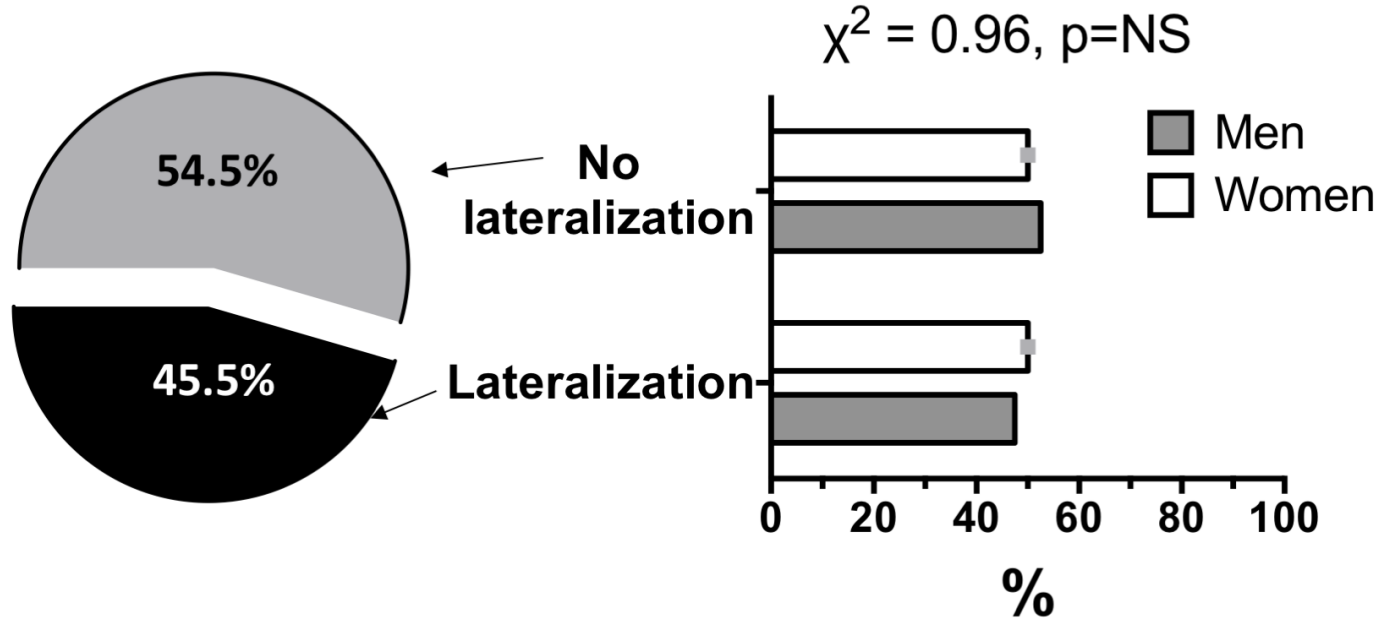

χ2 = 0.96, p=NS
54.5%
45.5%
No lateralization
Lateralization
Men
Women
0
20
40
60
80
100
%

Figure 2

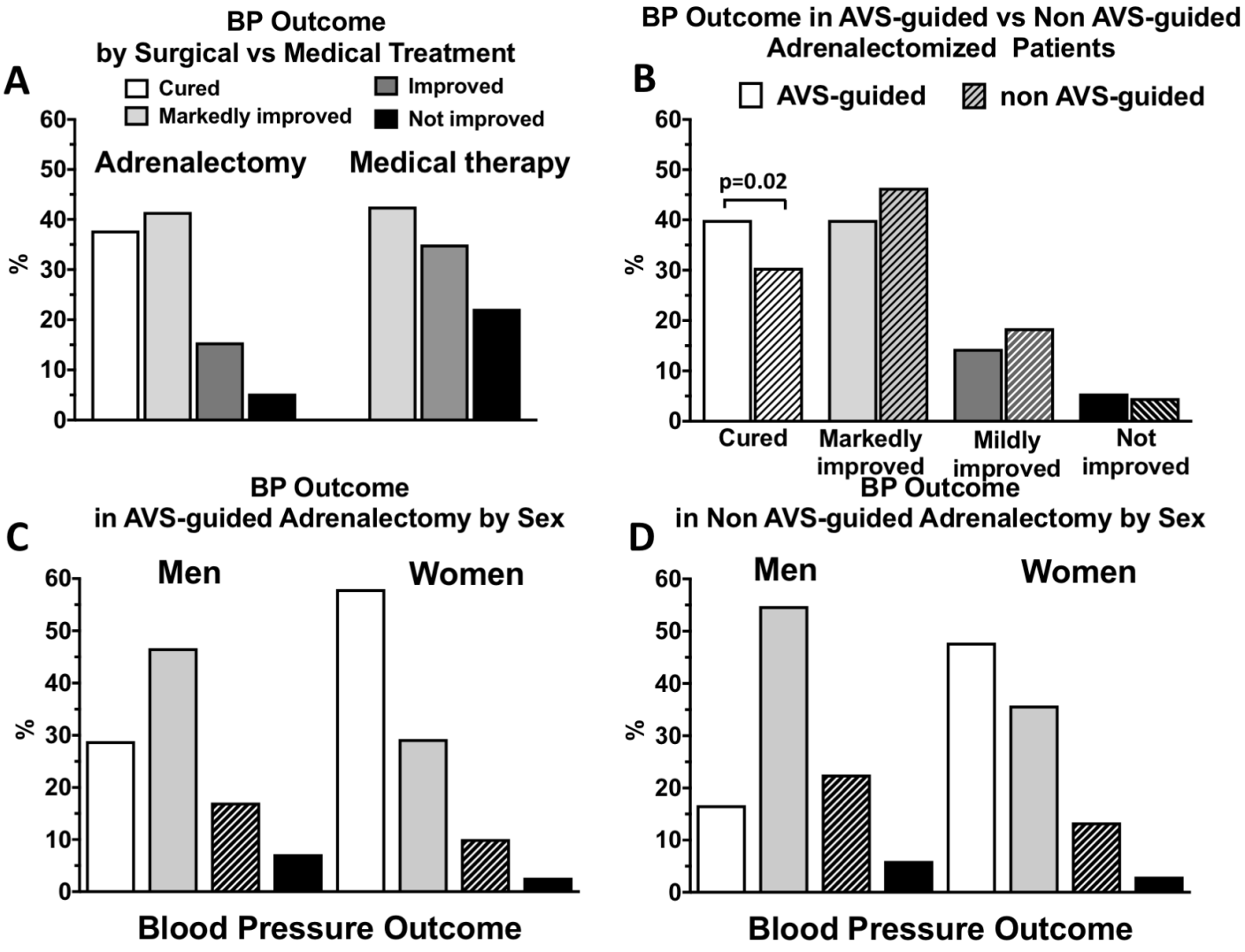

A
BP Outcome
by Surgical vs Medical Treatment
Cured
Markedly improved
Improved
Not improved
Adrenalectomy
Medical therapy
%
60
50
40
30
20
10
0
B
BP Outcome in AVS-guided vs Non AVS-guided
Adrenalectomized Patients
AVS-guided
non AVS-guided
p=0.02
Cured
Markedly improved
Mildly improved
Not improved
C
BP Outcome
in AVS-guided Adrenalectomy by Sex
Men
Women
Blood Pressure Outcome
D
BP Outcome
in Non AVS-guided Adrenalectomy by Sex
Men
Women
Blood Pressure Outcome

Figure 3

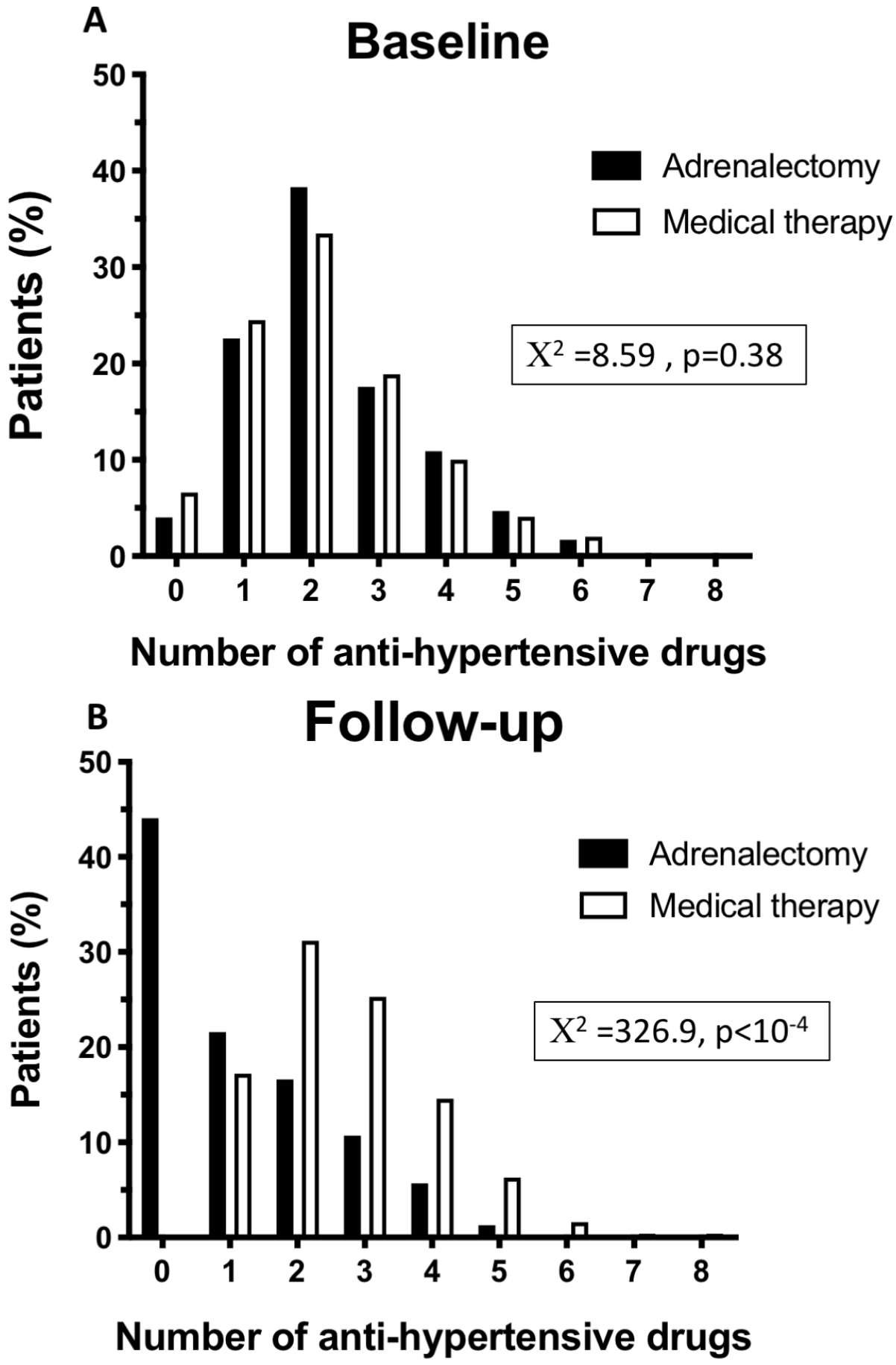

A
Baseline
Patients (%)
50
40
30
20
10
0
Adrenalectomy
Medical therapy
X² =8.59 , p=0.38
0 1 2 3 4 5 6 7 8
Number of anti-hypertensive drugs
B
Follow-up
Patients (%)
50
40
30
20
10
0
Adrenalectomy
Medical therapy
X² =326.9, p<10-4
0 1 2 3 4 5 6 7 8
Number of anti-hypertensive drugs

Figure 4

Antihypertensive drugs burden at follow-up in patients submitted to AVS-guided and non AVS-guided adrenalectomy

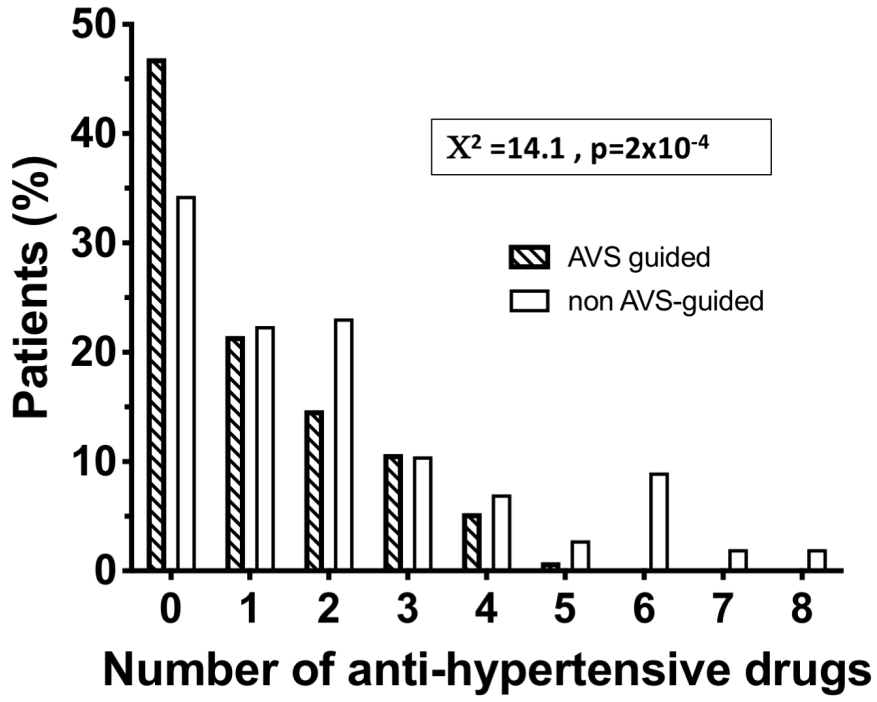


Figure 5