Drug-Resistant Hypertension

in A Large Registry of Primary Aldosteronism

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**Expanded methods; AVIS2 data collection form; Supplemental tables: 3**.

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**EXPANDED METHODS**

The AVIS-2 study was an observational multi-center study conceived in 2012 with the aim of creating a large database of individual adrenal vein sampling (AVS) studies performed worldwide. The original protocol was registered at clinicaltrials.gov (NCT01234220) and thereafter amended to reach the target recruitment number of 1500 patients PA patients submitted to AVS in the last 15 years (2000-2015).

**Center selection criteria**

Eligible centers were identified from those that had published in English on primary aldosteronism (PA) and/or AVS in the last decade following the PICO strategy (P, population = adults with PA; I, intervention = AVS; C, comparator = simultaneous AVS vs. sequential catheterization technique, use of cosyntropin testing vs. non-stimulated condition, use of bilaterally vs. unilaterally selective AVS results, use of absolute hormonal data vs. selectivity and lateralization indices; and O, outcome = the ways AVS was performed and interpreted, adrenal vein rupture) (24). Suitable studies were identified by computer-assisted database searches (PubMed database, U.S. National Library of Medicine) using the key words: aldosterone, primary aldosteronism (PA), endocrine hypertension, adrenal vein sampling, and the Boolean operator “AND”; scanning of reference lists; hand-searching of relevant journals; correspondence with authors of relevant reports and meeting presentations; and consultation with experts in the field.

All procedures were carried out according to the Helsinki Declaration. The protocol of the study was approved by the Ethics Committee of both the coordinating center and the participating centers.

**Inclusion/exclusion criteria**

After identification of the eligible centers the inclusion criteria were: a) age ≥ 18 years; b) center’s agreement to participate in the data collection; c) approval of the Ethics Committee. The only exclusion criteria were unwillingness of the lead investigator to participate in the study and/or lack of local Ethics Committee’s approval.

**Data collection and harmonization**

To warrant privacy protection data anonymization was systematically exploited in an *ad hoc* web-based platform ([https://fm.dmcs.unipd.it](https://fm.dmcs.unipd.it0)) and a predefined form (reported below), which was created for on-line data collection. High quality of the data was ensured by using appropriate filters to prevent input of values that were not biologically plausible and/or were in wrong unit of measures. Data were securely stored in a protected server at the coordinating center, which had full access to the dataset; each local lead investigator had access with username and password to the his/her center’s database.

**Summary List of the collected variables**

* Demography (sex 1 =M 2=F, weight, BMI, race, etc.);
* AVS date (MM/DD/YYYY);
* Birth date (MM/DD/YYYY);
* Calculated age at AVS = AVS date (MM/DD/YYYY)- Birth date (MM/DD/YYYY) in years;
* Systolic and diastolic blood pressure values (mmHg) at the time of AVS;
* Ongoing medical therapy at the time of AVS;
* Biochemical profile at baseline (sK+, plasma aldosterone concentration (PAC); plasma renin activity (PRA).
* AVS protocol (bilaterally simultaneous/sequential; stimulated/unstimulated).
* PAC and plasma cortisol concentration (PCC) in each adrenal vein and in the inferior vena cava blood;
* Concordance/discordance between imaging and AVS results.
* Treatment modality: right/left/bilateral laparoscopic adrenalectomy; medical treatment.
* Blood pressure outcome at 6-months defined as reported in Supplemental Table 2.
* Persistence /correction of hypokalaemia at follow-up.
* Serum K+, PAC and PRA at follow-up.
* Complications: adrenal vein rupture.
* Diagnosis (unilateral aldosterone-producing adenoma (APA); bilateral APA, unilateral adrenal hyperplasia; bilateral adrenal hyperplasia.

The conclusive diagnosis of unilateral PA required demonstration of biochemical cure at follow-up.

**Supplemental table 1: Pre-specified definitions of the BP outcome. The PASO criteria, which were proposed afterward based on expert consensus are also reported for comparison.**

|  |  |  |
| --- | --- | --- |
|  |  | ***PASO CRITERIA\**** |
| **Cure** | normotension (BP < 140/90 mmHg) without any antihypertensive agents. | *Complete clinical success* |
| **Marked improvement** | normotension on the same or reduced number of medications and BP similar to baseline but with a marked decreased (> 2 drugs) of medications. | *Partial clinical success* |
| **Mild improvement** | a fall of systolic and/or diastolic BP > 10%, but without achievement of normotension with the same or reduced therapy. |
| **No improvement** | no fall of systolic and/or diastolic BP and/or need for increased number and/or dose of antihypertensive medications. | *Absent clinical success* |

BP = Blood Pressure; \*PASO consensus from *Williams TA, Lancet Diabetes Endocrinol 2017; 5(9):689-699*, for comparison

**Supplemental table 2: Definitions of the AVS indexes.**

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| --- | --- | --- |
| **Index** | **Formula** | **Significance** |
| **Selectivity Index (SI)** |  | SI estimates the correct positioning of catheters in the adrenal vein |
| **Lateralisation Index (SI)** |  | LI measures the aldosterone secretion of the dominant over the contralateral adrenal gland corrected for the degree of selectivity and for blood dilution from extra-adrenal sources. |
| **Relative Aldosterone Secretion Index (RASI)** |  | RASI estimates the secretion of aldosterone  relative to cortisol from each adrenal gland, adjusted for the degree of selectivity (dilution).  In the nondominant side it equals the so-called ‘contralateral suppression index’ |

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PAC = plasma aldosterone concentration. PCC = plasma cortisol concentration. IVC = inferior vena cava. Dominant side = the side with higher RASI value.

**Supplemental Table 3: Demographic and clinical features of the cohort of 1197 patients with conclusive information on BP resistance to treatment according to each center’s lead investigator.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Whole cohort  (n=1197) | With Resistant Hypertension  (n=592) | Without Resistant Hypertension  (n=605) | P value for comparison between with/without Resistant Hypertension |
| Age (yrs) | 51.4 ± 10.9 | 53.0 ± 10.7 | 50.3. ± 10.9 | < 10-4 |
| Sex (M/F, %) | 742/455 (62/38) | 367/225 (62/38) | 345/260 (57/43) | = 5.8\*10-2 |
| Body Mass Index (Kg/m2) | 28.6 ± 5.4 | 30.5 ± 5.5 | 27.0 ± 4.8 | = 9\*10-3 |
| Systolic BP (mmHg) | 154 ± 20 | 160 ± 20 | 148 ± 19 | < 10-4 |
| Diastolic BP (mmHg) | 93 ± 13 | 95 ± 13 | 91 ± 12 | < 10-4 |
| Heart rate (beats/min) | 73 ± 12 | 73 ± 12 | 73 ± 12 | NS |
| Serum K+ (mmol/l) | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.4 ± 0.5 | < 10-4 |
| Hypokalemia at baseline (%) | 434 (36.3) | 214 (36.3) | 232 (38.3) | NS |
| Plasma Aldosterone Concentration (ng/dl) | 29.4 (28.1-30.7) | 32.2 (30.2-34.3) | 26.6 (25.1-28.1) | NS |
| Plasma Renin Activity (ng/ml/h) | 0.54 (0.49-0.59) | 0.55 (0.49-0.60) | 0.53 (0.46-0.60) | NS |
| ARR (ng/dL)(ng/mL/h) | 91 (86 – 96) | 98 (90 – 105) | 84 (77 – 90) | NS |
| N. drugs | 2.4 (2.3-2.5) | 3.2 (3.1-3.3) | 1.6 (1.5 – 1.7) | < 10-4 |
| N. drugs of follow-up | 1.9 (1.8 – 2.0) | 2.2 (2.1 – 2.4) | 1.6 (1.4 – 1.8) | 1.7\*10-2 |
| Ethnicity (%): Caucasians/Asians/  Africans & African American/Hispanics | 946/203/36/12  (79/17/3/1) | 527/41/18/6  (89/7/3/1) | 430/163/12/0  (71/27/2/0) | 10-6 |
| Maximum diameter of the detectable single nodule (mm) |  | 14 (10-19) |  |  |

Normal range on a Na+ between 100-300 mEg/day: PAC < 15 ng/dL; PRA : 0.65 – 2.65 ng/ml/h;: ARR: < 26 ng/dl/ng/ml/h.

Mean±SD or median and IQ range. Abbreviations: BP: blood pressure; PRA: Plasma renin activity; PAC: plasma aldosterone