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# 1            **A clinical prediction score to diagnose unilateral primary aldosteronism**

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1 **ABSTRACT**

2 **Context.** Adrenal venous sampling is recommended to assess whether aldosterone hypersecretion is  
3 lateralized in patients with primary aldosteronism. However, this procedure is invasive, poorly  
4 standardized and not available everywhere.

5 **Objective.** Our goal was to identify patients' characteristics that can predict unilateral aldosterone  
6 hypersecretion in some patients who could hence bypass adrenal venous sampling before surgery.

7 **Design.** Cross sectional diagnostic study performed from February 2009 to July 2010.

8 **Setting.** A single center specialized in hypertension care.

9 **Patients.** 101 consecutive patients with primary aldosteronism who underwent adrenal venous  
10 sampling. The autonomy of aldosterone hypersecretion was assessed with the saline infusion test.

11 **Intervention.** Adrenal venous sampling was performed without ACTH infusion but with simultaneous  
12 bilateral sampling.

13 **Main Outcome Measure.** Variables independently associated with a lateralized adrenal venous  
14 sampling in multivariate logistic regression were used to derive a clinical prediction rule.

15 **Results.** Adrenal venous sampling was successful in 87 patients and lateralized in 49. All 26 patients  
16 with a typical Conn's adenoma plus serum potassium  $< 3.5$  mmol/l or estimated glomerular filtration  
17 rate  $\geq 100$  ml/min/1.73m<sup>2</sup> (or both) had unilateral primary aldosteronism; this rule had 100%  
18 specificity [95% confidence interval: 91, 100] and 53% sensitivity [95% confidence interval: 38, 68].

19 **Conclusions.** If our results are validated on an independent sample, adrenal venous sampling could be  
20 omitted before surgery in patients with a typical Conn's adenoma if they meet at least one of two  
21 supplementary biochemical characteristics (serum potassium  $< 3.5$  mmol/l or estimated glomerular  
22 filtration rate  $\geq 100$  ml/min/1.73m<sup>2</sup>).

23

24

## 1 INTRODUCTION

2 Estimates of the prevalence of primary aldosteronism (PA) among non selected hypertensive adults  
3 range from 5% to 10%. Aldosterone hypersecretion affects sodium and potassium balance, increases  
4 blood pressure (BP) and induces target-organ damage (1). Adrenalectomy normalizes the plasma  
5 aldosterone to renin ratio (ARR) and serum potassium in all patient with unilateral PA, induces a large  
6 BP and/or medication reduction in the majority – even if hypertension is cured in only 40% of cases –  
7 and improves markers of target-organ damage like left ventricular hypertrophy or microalbuminuria  
8 (2).

9 Adrenal imaging can show a typical Conn's adenoma in case of unilateral PA but adrenal venous  
10 sampling (AVS) is the recommended procedure to differentiate between unilateral and bilateral  
11 primary aldosteronism (3, 4). The main reason to promote a systematic use of AVS is that the results  
12 of imaging studies often disagree with the results of AVS (5).

13 However, published studies on adrenal imaging in PA have many shortcomings. Most importantly,  
14 they seldom provide sufficient information to judge which one is right when imaging and AVS  
15 disagree. Moreover, comparisons between imaging studies and AVS are performed without taking  
16 patients' age into account. Several experts assert that typical Conn's adenoma on imaging ( $\geq 10$  mm)  
17 and lateralized AVS match well in patients  $\leq 40$ -year old, since adrenal incidentaloma is rare in this  
18 age group (6). This view has been endorsed by a consensus panel (4). A few experts even claim that  
19 AVS is unneeded in patients of any age with PA and a typical Conn's adenoma ( $\geq 10$  mm), since they  
20 experience similar or even better surgical outcomes than patients who undergo adrenalectomy after  
21 documentation of unilateral aldosterone hypersecretion by AVS (7).

22 Regardless of its diagnostic value, AVS has several drawbacks (8). First, it is invasive and difficult to  
23 perform, with a complication rate of 0.2 to 13% and a failure rate of 2 to 60% (9). Second, the  
24 technical details of the procedure and the criteria used to interpret the results are not standardized (10-  
25 12). Third, AVS is not available everywhere and costly. Referral centers are able to perform only a  
26 few hundreds of AVS at most each year. They will be unable to meet the demand induced by broad

1 screening for PA even in high income countries, unless AVS is avoided in a significant number of  
2 cases (8).

3 Our objective was to determine whether lateralized AVS can be predicted from simple clinical,  
4 biological and radiological characteristics in the largest possible number of patients with PA.

5

## 6 **PATIENTS AND METHODS**

### 7 *Patients*

8 According to the Endocrine Society guidelines (3), the diagnosis of PA is ascertained by persistently  
9 high plasma aldosterone concentration (PAC) after a suppression test. Our local diagnostic criteria do  
10 not rely on suppression tests but on repeatedly elevated ARR and high baseline plasma and/or urinary  
11 aldosterone (13). However, following guidelines publication, we systematically perform a saline  
12 infusion test (SIT) in patients who are candidates for AVS since March 2009.

13 This retrospective study includes all patients who underwent AVS in our institution from March 2009  
14 to July 2010 and fulfilled either our diagnostic criteria or those recommended by the Endocrine  
15 Society guidelines (3). Patients were retrieved by querying the radiology and lab test results databases.

16 All AVS were performed by the same radiologist (AR).

17 Several patients were referred to our center for AVS after PA had been diagnosed elsewhere.

18 According to hormonal measurement performed in our center, some of these patients neither fulfilled  
19 our diagnostic criteria nor those recommended by the guidelines and were not included in the current  
20 study.

21

### 22 *Collected data and diagnostic criteria*

23 Baseline clinical features were systematically recorded during the first consultation: sex, current age  
24 and age at hypertension onset, body mass index (BMI, kg/m<sup>2</sup>). Trained nurses used a validated semi-  
25 automatic manometer (Omron 705CP) to determine blood pressure (BP) levels. Three measurements  
26 of blood pressure were obtained in the sitting position after a 5-minute rest period before  
27 measurements. Office blood pressure was determined by calculating the average from the three  
28 measurements.

1 Patients were then hospitalized for standardized hormonal assessment. Antihypertensive medications  
2 that interfere with the renin – angiotensin – aldosterone system (RAAS) were discontinued at least 2  
3 weeks before hospitalization (6 weeks for aldosterone and renin antagonists). Patients with high grade  
4 hypertension were prescribed a treatment bridge with verapamil and/or prazosine. However, about  
5 25% of patients in our institution are investigated without stopping all interfering drugs due to safety  
6 concerns (14). This compares favorably with recent series where up to 40% of patients had to be  
7 explored with interfering drugs (15). Three to six grams of potassium chloride daily were prescribed  
8 when serum potassium was less than 3.5 mmol/L.

9 Plasma active renin was determined by chemiluminescent immunoassay (LIAISON®, Diasorin).  
10 Plasma and urinary aldosterone concentrations were determined by radioimmunoassay (Coat-A-  
11 Count®, Siemens Medical Solutions Diagnostics). Urinary aldosterone was measured as the sum of  
12 free aldosterone and aldosterone from the hydrolysis of aldosterone 18-glucuronide at pH 1. The  
13 concentrations of plasma sodium, potassium and creatinine measured on the first sample collected  
14 during hospitalization were used for the analyses.

15 Our local criteria for the diagnosis of PA are based on the combination of (i) an ARR at least twice >  
16 64 pmol/mU, plus (ii) baseline supine plasma aldosterone > 500 pmol/l or baseline sitting/standing  
17 plasma aldosterone > 550 pmol/L or urinary aldosterone > 63 nmol/day. The active renin  
18 concentration is set at a minimum of 5 mU/l for the calculation of the ARR, to avoid inflating the ratio  
19 when active renin levels are very low.

20 For the SIT, plasma aldosterone concentration was determined in the supine position before and after  
21 the infusion of 2 L of saline over 4 hours, from 8:00 to 12:00 am. Aldosterone hypersecretion was  
22 considered non-suppressible if post-infusion plasma aldosterone was > 139 pmol/l (5 ng/dl). Higher  
23 cutoff values may miss many unilateral PA (16).

24 All patients underwent thin slice CT scan. Typical unilateral adenoma was defined as a unilateral  
25 radiolucent nodule (< 10 Hounsfield units on noncontrast) with a diameter  $\geq$  8 mm, with the remaining  
26 ipsilateral and contralateral glands appearing smooth and not enlarged. Of note, experts who advocate  
27 adrenal imaging as a possible surrogate for unilateral PA have been more conservative and used a  
28 diameter  $\geq$  10 mm (6, 7).

1 During AVS, aldosterone and cortisol concentrations were measured from samples taken  
2 simultaneously from both adrenal veins using two catheters. Bilateral simultaneous sampling is as  
3 effective as continuous adrenocorticotropic hormone stimulation to avoid time dependent variability of  
4 hormonal measurements (17). AVS was considered successful if plasma cortisol concentrations were  
5 at least twice as high in both adrenal veins as in the inferior vena cava. Ratios of aldosterone to  
6 cortisol concentration were calculated on each side. The lateralization ratio was computed as the  
7 highest adrenal aldosterone:cortisol ratio divided by the lowest one. We used a cutoff at 4 to  
8 categorize the patients as lateralized or not for statistical analyzes, as recommended by guidelines (3).

9

#### 10 *Statistical analysis*

11 We first assessed whether a typical Conn's adenoma  $\geq 10$  mm can be regarded as a good surrogate for  
12 ipsilateral aldosterone hypersecretion in all patients and in those  $\leq 40$ -year old.

13 Then we derived a new prediction rule to identify patients with unilateral aldosterone hypersecretion.

14 We used non parametric tests (Fisher's exact test for categorical variables and Mann-Whitney test for  
15 quantitative variables) to study bivariate associations, in all patients with a successful AVS, between  
16 the baseline clinical, biochemical and radiological characteristics on one hand and the outcome of  
17 AVS on the other hand.

18 Variables associated with lateralized AVS in bivariate analysis ( $p < 0.2$ ) were entered in multivariable  
19 logistic regression models. The linear relationship between the logit and quantitative independent  
20 variables was graphically checked in bivariate models. Stepwise forward selection was then performed  
21 to find variables independently associated with lateralized AVS (Wald test  $p < 0.05$ ). All first order  
22 interactions between these variables were tested.

23 The final logistic model was simplified to a clinical prediction score, with variables weighted  
24 according to their regression coefficients. C-statistic and ROC curves were used to evaluate the  
25 discrimination ability of regression models and of the prediction score to predict lateralized AVS.

26 Since physicians are reluctant to use prediction rules that do not perfectly predict what they are  
27 intended to (18), the diagnostic properties of the prediction score were computed for the cutoff value

1 with the best sensitivity among those that achieved 100% specificity. In case of a zero value in the 2 x  
2 table, 0.5 was added to each cell to compute the likelihood ratios and their confidence intervals.  
3 Statistical analyses were performed in Stata 9.2 SE for Windows.

4

## 5 **RESULTS**

### 6 *Patients*

7 Database retrieval yielded 116 AVS in 116 patients during the study period (Figure 1). Of these 116  
8 patients, 15 (13 %) fulfilled neither our diagnostic criteria nor those recommended by the guidelines.  
9 The remaining 101 patients were included: 61(60 %) met our and the Endocrine Society guidelines PA  
10 criteria; 14 (14 %) met our but not guidelines PA criteria; 8 (8 %) patients met guidelines but not our  
11 PA criteria; and 18 patients met our PA criteria but did not undergo SIT before AVS. Reasons not to  
12 perform a SIT before AVS were: kalemia repeatedly  $< 2.8$  mmol/l despite potassium supplementation  
13 (n=8, 44 %), systolic blood pressure (SBP) repeatedly  $\geq 180$  mmHg despite antihypertensive  
14 medication (n=4, 17 %), heart disease (n=2, 6 %), estimated glomerular filtration rate (eGFR)  $< 30$   
15 ml/min/1.73m<sup>2</sup> (n=1, 11 %), patient refusal (n=2, 11 %), and logistical reasons (n=2, 11 %). Some  
16 patients had more than one reason not to undergo the SIT.

17 Characteristics of the 101 included patients are provided in the Table 1: 14 had an unsuccessful AVS  
18 according to our criteria. Subsequent statistics were performed on the 87 patients with a successful  
19 AVS. Of these patients, 49 (56%) had a lateralization ratio  $\geq 4$ ; the proportion did not differ according  
20 to which diagnostic criteria was or were satisfied among guidelines criteria, local criteria or both (p =  
21 0.51). Only two variables among those reported in Table 1 had over 5% missing values: urinary  
22 aldosterone (6%) and post-SIT plasma aldosterone (18%).

23

### 24 *Diagnostic value of a typical Conn's adenoma on imaging*

25 Concordance of imaging and AVS is displayed in Table 2A for patients  $\leq 40$ -year old and Table 2B  
26 for patients  $> 40$ -year old.



1 Regardless of patients' age, a typical adenoma  $\geq 10$  mm on CT-scan had a specificity of 87% [95%  
2 CI: 72, 96] and a sensitivity of 55% [95% CI: 40, 69] to predict lateralized AVS in our population.  
3 Using this surrogate to indicate surgery would have avoided 26 AVS in our 87 patients, but 6 of them  
4 would have undergone surgery despite a lateralization ratio  $< 4$  (5 patients) or  $\geq 4$  but toward the other  
5 side (1 patient).

6 In patients  $\leq 40$ -year old, the specificity of a typical Conn's adenoma  $\geq 10$  mm was 100% [95% CI:  
7 91, 100] but sensitivity was only 18% [95% CI: 9, 32]. In other words, all patients  $\leq 40$ -year old with  
8 an adenoma  $\geq 10$  mm had a lateralized AVS on the ipsilateral side, but there were only 9 of those  
9 patients.

10

### 11 *Logistic models*

12 Comparisons of clinical and biological characteristics of patients with a lateralization ratio  $\leq$  or  $> 4$  are  
13 reported in Table 1. Patients with bilateral PA differed significantly from those with unilateral PA  
14 regarding the following variables: body mass index (BMI), systolic and diastolic BP, serum sodium  
15 and potassium concentrations, eGFR, plasma aldosterone, plasma renin and their ratio, and typical  
16 adenoma on imaging.

17 A multivariable logistic regression model was built to predict the outcome of AVS when it was  
18 successful. Three variables entered in the model by forward stepwise selection: typical Conn's  
19 adenoma, hypokalemia ( $< 3.5$  mmol/l) and eGFR in patients. There was no first order interaction  
20 between these three variables. There was also no interaction between the prescription of potassium  
21 supplements (3 to 6 g/d) and the predictive value of hypokalemia. The coefficients of the three-  
22 variable model are reported in Online Supplement Table A. The model had a good fit (Hosmer-  
23 Lemeshow  $\chi^2$  5.7 with 6 degrees of freedom,  $p = 0.46$ ) and a good discrimination ability (c-statistic of  
24 0.84). The discrimination was not improved by saturating the model with a hormonal variable  
25 reflecting the intensity of aldosterone hypersecretion (baseline level) or its autonomy (ARR or  
26 aldosterone level after saline infusion).

1 To simplify the derivation of a prediction score, eGFR was classified according to its tertiles: < 80  
2 ml/min/1.73m<sup>2</sup>; 80 to 100 ml/min/1.73m<sup>2</sup>; and ≥ 100 ml/min/1.73m<sup>2</sup>. These categories have been  
3 coded as 0, 1 and 2, respectively, after verification of the linearity assumption. The fit of the simplified  
4 logistic model remained good (Hosmer-Lemeshow  $\chi^2$  6.9 with 5 degrees of freedom, p = 0.23), as did  
5 its discrimination ability (c-statistic 0.87). The coefficients of the simplified model are reported in  
6 Online Supplement Table B.

7

### 8 *Prediction score and prediction rule*

9 A prediction score was built from the regression coefficients and is displayed in Table 3. The  
10 maximum score is 7 points: the higher the score, the higher the probability of lateralization. The area  
11 under the ROC curve of the prediction score was 0.86 [95% CI: 0.78, 0.94] (Figure 2).

12 The lowest threshold above which the score was perfectly specific was 5. Subjects with a score ≥ 5  
13 were those with a typical Conn's adenoma plus serum potassium < 3.5 mmol/l or eGFR ≥ 100  
14 ml/min/1.73m<sup>2</sup> (or both). This criterion had a specificity of 100% [95% CI: 91, 100] and a sensitivity  
15 of 53% [95% CI: 38, 68] to predict a lateralized AVS. After adding 0.5 to each cell of the table, the  
16 positive likelihood ratio was 41.3 [95% CI: 2.6, 657] and the negative likelihood ratio 0.48 [95% CI:  
17 0.35, 0.64]. Using this criterion as a surrogate, 26 patients (30%) would have been correctly identified  
18 as lateralized without the need for AVS. The lateralization ratio of these 26 patients ranged from 6.8 to  
19 117. Of note, all patients ≤ 40-year old with a typical adenoma ≥ 10 mm were also identified by this  
20 criterion.

21

## 22 **DISCUSSION**

### 23 *Summary of findings*

24 Our results confirm that having a typical Conn's adenoma ≥ 10 mm is not always associated with  
25 unilateral aldosterone hypersecretion and may not be regarded, alone, as a sufficient feature to indicate  
26 surgery. However, in patients ≤ 40-year old, it seems to be an accurate surrogate for unilateral

1 aldosterone hypersecretion, as advocated by some experts and some guidelines (4, 6). However, the  
2 number of patients with PA who could avoid AVS thanks to this rule is only about 10%.

3 Our results suggest that patients with PA and a typical Conn's adenoma  $\geq 8$  mm on CT scan can be  
4 considered as having unilateral aldosterone hypersecretion if they also have serum potassium  $< 3.5$   
5 mmol/l (regardless of the prescription of potassium supplements) and/or eGFR  $\geq 100$  ml/min/1.73m<sup>2</sup>.  
6 If this rule is validated, as much as 30% of PA patients could avoid AVS and be directly diagnosed  
7 with unilateral PA.

8

### 9 *Strengths and limitations*

10 Firstly, the number of included patients is limited but they were diagnosed in recent years and are  
11 representative of current PA patients. Secondly, the design of this study is retrospective but patients  
12 underwent a thorough standardized assessment and clinical and biochemical data were prospectively  
13 recorded in a structured electronic form used for patient care. Consequently, the only variable with  
14 more than 10% missing values was post-SIT plasma aldosterone because the test was not feasible in  
15 several patients. Thirdly, biochemical studies were performed during the first diagnostic work-up, with  
16 potassium supplements when indicated and without interfering anti-hypertensive drugs when possible.  
17 Only values recorded in similar conditions should be used to compute the score. Fourthly, the MDRD  
18 equation is regarded as inaccurate for eGFR  $> 60$  ml/min/1.73m<sup>2</sup>, unlike the CKD-EPI equation (19).  
19 Consequently, we tried to use the CKD-EPI equation but the fit of logistic models was not better. We  
20 therefore stayed to the MDRD equation, which is more readily available. **Fifthly**, we considered  
21 Conn's adenomas to be typical only if the remaining ipsilateral and contralateral glands appeared  
22 smooth and not enlarged. This is known to increase the specificity of imaging (20, 21) and must also  
23 be observed when computing the score. **Sixthly**, AVS result is only a surrogate but it is currently  
24 regarded as the most reliable indicator of unilateral PA, according to which surgical decisions are  
25 taken. Lastly, our diagnostic procedures and definitions may differ from those used in other centers. In  
26 this case, physicians should ascertain that our rule applies for their patients before adopting it for  
27 routine care.

28

1 *Comparison with previous studies and interpretation*

2 Previous studies have looked for alternatives to AVS to ascertain unilateral aldosterone hypersecretion  
3 in patients with PA. Stimulation tests have been used for this purpose, assuming that aldosterone  
4 secretion is somewhat responsive to angiotensin II in bilateral PA but not in unilateral PA. However, a  
5 significant proportion of aldosterone producing adenomas appear to be angiotensin responsive and  
6 recent studies have shown that the postural stimulation test is not accurate enough to guide surgical  
7 decision (21-23). Nonetheless, the diagnosis of unilateral PA seems to be very likely when both a  
8 typical adenoma is seen on imaging and the postural stimulation test is positive (24, 25). A recent  
9 study also suggests that the response to stimulation with ACTH may be more discriminatory (26).  
10 Radionuclide scintigraphy with <sup>131</sup>I-iodocholesterol (including NP59) has been used to determine  
11 PA subtype. The diagnostic value of this test has been challenged (27, 28), even if studies suggest that  
12 an adenoma on imaging is specific of unilateral PA when associated with scintigraphic uptake on  
13 single-photon emission CT (SPECT) (29). Physicians will remain reluctant to use this test because the  
14 procedure is very demanding (ACTH inhibition by dexamethasone taken days before and after the  
15 tracer injection, saturation of thyroid cells with potassium iodide before the injection, blockage of the  
16 enterohepatic cycle of the tracer with a bile salt chelator and/or a laxative, images taken between 4 and  
17 9 days after the injection) and the radiation dose is high (about 60 mSv). Recently, <sup>11</sup>C-Metomidate  
18 positron emission tomography (PET)-CT has been proposed to overcome the delay between injection  
19 and imaging, but dexamethasone pretreatment is still needed, the tracer is not widely available yet  
20 (30).

21 We wanted to build on readily available data to derive our prediction score and the result of adrenal  
22 CT scan was a natural candidate. As already mentioned numerous studies have reported discrepancies  
23 between imaging and AVS and taken this evidence as a failure of imaging. However, AVS also can  
24 fail and indicate unilateral PA in patients who are subsequently not hormonally cured by  
25 adrenalectomy (12, 31-33), or indicate bilateral PA in patients who are subsequently hormonally cured  
26 by adrenalectomy (34, 35).

27 Several teams use AVS only when imaging does not show a typical Conn's adenoma and have  
28 reported similar (33, 36, 37), or even better (31, 38), surgical outcomes in patients who were sent to

1 surgery on this ground rather than following lateralized AVS. However, patients with unilateral PA  
2 may have a better surgical outcome when they have a typical adenoma than when they do not. This  
3 may have outweighed a few patients with bilateral PA that were wrongly sent to surgery despite a  
4 typical but non secreting adenoma.

5 Currently, evidence seems still too weak to recommend sending all PA patients with a typical Conn's  
6 adenoma to surgery, even with stringent radiological criteria as ours. Our result confirm that imaging  
7 and AVS can disagree, but also show that false positives of imaging (typical adenoma without  
8 ipsilateral aldosterone hypersecretion) are probably limited to patients over 40-year old. This confirms  
9 the experience of other teams (4, 6, 23).

10 The present study suggests that hypokalemia and relative glomerular hyperfiltration support the  
11 diagnosis of unilateral aldosterone hypersecretion in patients with PA and a typical adenoma on  
12 imaging. There is prominent evidence that hypokalemia is more frequent in patients with unilateral PA  
13 than in patients with bilateral PA, even since the advent of the aldosterone to renin ratio to more  
14 systematically screen for PA (13, 22, 23, 39). There is also mounting evidence that patients with PA  
15 have a relative glomerular hyperfiltration compared to patients with essential hypertension (40).  
16 However, only few data hinted that this relative hyperfiltration may be more prominent in patients  
17 with aldosterone producing adenomas than in those with bilateral PA (13), and several previous  
18 studies failed to find a difference between the two subtypes in this regard (22, 41, 42). Nonetheless, it  
19 is plausible that more severe aldosteronism in our patients with lateralized PA induced more marked  
20 intrarenal hemodynamic adaptation (43), besides lower serum potassium concentrations due to greater  
21 urinary potassium losses.

22

### 23 *Conclusion*

24 We confirmed that a typical adenoma  $\geq 10$  mm on a CT scan in a 40-year old or younger patient is  
25 always associated with lateralized AVS. Moreover, our results suggest that AVS could be omitted in  
26 patients with a typical Conn's adenoma  $\geq 8$  mm if they have serum potassium  $< 3.5$  mmol/l and/or  
27 eGFR  $\geq 100$  ml/min/1.73m<sup>2</sup>. If this rule is validated on an independent sample, these patients could

1 undergo surgery directly, without need for AVS, which is an invasive and not widely available test.  
2 Based on current knowledge, patients with PA who do not have a typical adenoma on CT scan or who  
3 do not meet one of the aforementioned additional characteristics should still undergo AVS before  
4 surgery.

5

## 6 **ACKNOWLEDGMENTS**

7 None

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1

2 **FIGURE LEGENDS**

3

4 **Figure 1.** Patient selection and distribution.

5 AVS, adrenal vein sampling; PA, primary aldosteronism; SIT, saline infusion test

6

7 **Figure 2.** Receiver operating characteristic (ROC) curve of the clinical prediction score.

8

## TABLES

Table 1. Baseline characteristic of included patients

	Unsuccessful AVS (n=14)	Successful AVS (n=87)	p value	Lateralized AVS (n=49)	Non-lateralized AVS (n=38)	p value
Male patients	6 (43%)	53 (61%)	0.25	27 (55%)	26 (69%)	0.27
Age , y	48 [42, 57]	46 [39, 51]	0.26	45 [36, 50]	47 [40,51]	0.39
Familial hypertension	10 (59%)	49 (59%)	0.36	28 (57%)	21 (62%)	0.82
Duration of hypertension, y	11.5 [5, 21]	4 [2, 12]	0.02	4 [2, 10]	6 [2, 14]	0.65
Body mass index, kg/m <sup>2</sup>	24.3 [23.4, 28.9]	28.2 [25.1, 31.4]	0.07	26.3 [24.7, 29.5]	29.4 [26.9, 31.7]	0.05
Systolic BP, mmHg	138.5 [132, 157]	141 [128, 155]	0.64	138 [127, 148]	144 [134, 169]	0.06
Diastolic BP, mmHg	85.5 [79, 91]	87 [78, 97]	0.94	85 [76, 95]	90 [82, 100]	0.09
Antihypertensive drug classes	2 [1, 3]	2.5 [2, 3]	0.36	2 [1, 3]	3 [2, 4]	0.26
Potassium supplement (3000 to 6000 mg)	6 (43%)	27 (31%)	0.38	17 (35%)	10 (26%)	0.49
Serum potassium, mmol/l	3.35 [2.9, 3.5]	3.4 [3, 3.6]	0.71	3.2 [2.8, 3.5]	3.6 [3.2, 3.7]	<0.001
Serum potassium < 3.5 mmol/l	7 (50%)	49 (56%)	0.77	35 (71%)	14 (37%)	0.002
Serum sodium, mmol/l	141.5 [139, 143]	140 [139, 142]	0.56	141 [140, 142]	140 [139, 142]	0.04

Estimated GFR, ml/min/1.73m <sup>2</sup>	91 [84, 101]	89 [77, 108]	0.85	100 [85, 120]	82 [66, 91]	<0.001
Baseline active renin, mU/l	2.5 [0.5, 3.6]	1.8 [1.2, 4.4]	0.60	1.5 [0.5, 4.1]	2.7 [1.6, 4.6]	0.02
Baseline PAC, pmol/l	1014 [569, 1473]	587 [397, 894]	0.08	634 [446, 1065]	523 [373, 663]	0.04
Baseline ARR, pmol/mU	203 [114, 295]	113 [73, 168]	0.05	126 [85, 207]	95 [66, 123]	0.01
Urinary aldosterone, nmol/d	112 [71, 158]	83.5 [55, 126]	0.32	85 [52, 132]	82 [56, 125]	0.92
Post-SIT PAC, pmol/l	338 [148, 1030]	225 [162, 445.5]	0.62	368 [191, 486]	189 [152, 332]	0.009
Adenoma ≥ 8 mm on CT	8 (57%)	36 (41%)	0.39	30 (61%)	6 (16%)	<0.001

Reported values are numbers (percentages) or median [p25, p75].

No: number of observations; y: years; BP: blood pressure; GFR: glomerular filtration rate; PAC: plasma aldosterone concentration; ARR: aldosterone to renin ratio; AVS: adrenal venous sampling; SIT: sodium infusion test; CT: computed tomography scan.

Table 1. Concordance of adrenal venous sampling and imaging results in patients  $\leq$  or  $>$  40-year old with primary aldosteronism

A. Patients $\leq$ 40-year old Typical Conn's adenoma $\geq$ 10 mm on CT scan	AVS results			Total
	Unilateral right	Unilateral left	Bilateral	
Right adrenal	2	0	0	2
Left adrenal	0	7	0	7
None	5	1	10	16
Total	7	8	10	25

  

B. Patients $>$ 40-year old Typical Conn's adenoma $\geq$ 10 mm on CT scan	AVS results			Total
	Unilateral right	Unilateral left	Bilateral	
Right adrenal	9	1	4	14
Left adrenal	0	8	1	9
None	8	8	23	39
Total	17	17	28	62

AVS, adrenal vein sampling; CT, computed tomography

Table 3. Clinical prediction score to predict lateralized adrenal venous sampling (higher score indicates higher probability of lateralized adrenal venous sampling).

Item	Points
Typical Conn's adenoma on imaging	3 points
Hypokalemia < 3,5 mmol/l	2 points
eGFR (MDRD)	
< 80 ml/min/1.73m <sup>2</sup>	0 point
80 to 100 ml/min/1.73m <sup>2</sup>	1 point
≥ 100 ml/min/1.73m <sup>2</sup>	2 points
<b>Total score</b>	<b>(maximum 7 points)</b>

eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.