Online-only supplement

Computed tomography and adrenal venous sampling in the diagnosis of unilateral primary aldosteronism

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Expanded Methods Section

Patient cohorts

All 12 centres from the PASO study were invited to contribute patient data based on AVS surgical management, of which 9 accepted (Berlin, Brisbane, Kyoto, Ljubljana, Munich, Sendai, Torino, Warsaw, Yokohama).[1] A few of these centres also submitted data based on CT surgical management (Ljubljana, Torino, Warsaw) from patients who either refused AVS or from those with an unsuccessful AVS (failed cannulation of both adrenal veins). To exclude management bias in the unsuccessful AVS cases: CT results from patients with partial AVS data with information of diagnostic relevance were excluded (in particular, suppressed aldosterone production in the cannulated adrenal vein, which is suggestive of unilateral aldosterone production confined to the contralateral adrenal).[2] Additional centres contributed data from patients whose management was based on CT scan (Ancona, Padua, Prague, Santiago, Sofia, Thessaloniki, Trieste, Udine, Würzburg) (Table S1). Data from 761 patients with unilateral primary aldosteronism were obtained (235 with CT management diagnosed from 1994 to 2016, and 526 with AVS management diagnosed from 1994 to 2015) (Table S1). Clinical and biochemical outcomes were assessed retrospectively in accordance with the standardised criteria of the PASO

consensus with follow-up at 6-12 months.[1] PA was diagnosed by the US Endocrine Society guideline or the Japan Endocrine Society guideline.[3, 4]

The patients underwent adrenal CT scan with contrast and fine cuts (< 3 mm) using standard criteria for adrenal gland investigations including noncontrast CT attenuation measured in Hounsfield units.[5] The CT group included all patients in each centre with a diagnosis of unilateral PA by CT in the study period (Figure S1). In this group, unilateral primary aldosteronism was diagnosed if a unilateral nodule of at least 8 mm in diameter was detected. The timelines of the diagnoses of patients with absent or partial biochemical outcome following adrenalectomy in the CT group are shown in Figure S1. For both groups, adrenalectomy was performed by expert endocrine surgeons and there were no pathology reports of incomplete removal of adrenals.

Patient data were obtained with appropriate approval from local ethics committees and written informed patient consent was obtained for data collection in all centres except Kyoto and Yokohama City because in Japan in accordance with the Ethical Guidelines for Medical and Health Research involving human subjects informed consent is not mandatory for research that does not involve the use of human biological specimens.

Outcome assessment

Blood pressure was measured in accordance with the ESH/ESC (European Society of Hypertension/European Society of Cardiology) Guidelines for the management of arterial hypertension using a mercury sphygmomanometer or other validated device.[6] Baseline blood pressure (BP) was measured at the first visit under treatment and post-surgical BP at 6-12 months after adrenalectomy. AVS protocols were variable with 4 centres (n=273 patients) using an unstimulated procedure and 5 centres (n= 253 patients) using ACTH infusion, further details of AVS and interpretation of results are provided in Williams et al.[1] Renin and aldosterone measurements were as described previously.[1, 2] Clinical and biochemical outcomes were assessed at 6-12 months using the PASO criteria and are based on blood pressure measurements and antihypertensive drug dosage (clinical outcome) and hormonal (aldosterone and renin) and potassium measurements (biochemical outcome).[1] Each centre participating to the study calculated outcome data for their cohort which was cross-checked by a participant from a different centre (TAW, JB and MR).

Clinical outcomes could be overestimated in patients treated with mineralocorticoid antagonists (a targeted treatment for PA) at follow-up in cases of persisting PA (absent or partial biochemical success). In this study, 4 of the 761 patients had mineralocorticoid antagonist treatment at follow-up: 1 from the CT scan group (with a complete biochemical and partial clinical outcome) and 3 from the AVS group (2 patients with complete biochemical and absent clinical success; 1 patient with partial clinical and partial biochemical success). Therefore, there was a possible confounding effect of MRA therapy at follow-up on the clinical outcome of a single patient from the AVS group with partial biochemical success in whom the partial clinical outcome reflects treatment of PA by surgery and also by specific medical treatment.

Statistical analyses

Categorical variables are described as absolute numbers and percentages, quantitative normally distributed variables are reported as means with SDs and non-normally distributed variables as medians with IQRs. A one-way ANOVA with a post hoc Bonferroni correction was used to analyse quantitative normally distributed variables. Group differences were assessed by Kruskal-Wallis or Mann-Whitney *U* tests for quantitative non-normally distributed variables or, for categorical variables, by a chi-square or Fisher's exact test. Multinomial logistic regressions were used to identify factors associated with clinical and biochemical outcomes and parameters included in models were selected for clinical relevance. An adjusted OR greater than 1 indicates an increased likelihood of a clinical or biochemical outcome (complete *versus* partial + absent, complete + partial *versus* absent or complete *versus* absent) and an adjusted OR less than 1 indicates a decreased likelihood. An exception is for plasma potassium concentrations which were analysed for lowest values and therefore an OR less than 1 indicates an increased likelihood. An elevated ARR_PRA (aldosterone-to-renin ratio_plasma renin activity) was defined as an ARR > 65 with plasma aldosterone concentrations in pmol/L and plasma renin activities in pmol/L/min. An elevated ARR_DRC (aldosterone-to-renin ratio_direct renin concentration) was defined as an ARR > 102.6 with direct renin concentrations in mU/L. ARR reference limits were based on the most commonly used cutoff values reported in the Endocrine Society guideline.[3] IBM SPSS statistics version 22.0 was used for all analyses. P values <0.05 were considered significant.

Expanded Results section

Clinical variables of patients stratified by CT or AVS based management

Clinical parameters at baseline and follow-up showed that patients in the CT and AVS groups had a similar mean age at surgery (49.3 ± 11.3 years and 50.9 ± 11.0 years in the CT and AVS groups, respectively) whereas the CT scan group comprised a significantly greater proportion of females (56.2% in the CT scan group *versus* 46.6% in the AVS group, p=0.014) and had a larger estimated tumour size at imaging (16 mm diameter, IQR 11.0-22.0 *versus* 13 mm, 8.8-17.0, p<0.001). Systolic blood pressure levels were significantly higher in the CT than the AVS group both at baseline and follow up (p<0.001) (Table 1).

In the total cohort, the diagnostic approach had no discernable effect on post-operative changes in systolic blood pressure (26 mm Hg ± 18.3 *versus* 23 mm Hg ± 22.4 in the CT and AVS groups, respectively, p= 0.140) and anti-hypertensive medication ([1.5 DDD, IQR 0.7-2.5] *versus* [1.5 DDD, IQR 0.5-3.0], CT and AVS groups, respectively, p=0.508) (Table 1). There was a significant difference in diastolic blood pressure change (16 mm Hg ± 12.3 *versus* 11 mm Hg ± 14.2 in the CT and AVS groups, respectively, p< 0.001) (Table 1).

Table S1. Centres participating to the study with surgical decision based on CT or AVS

CT group		AVS group	
Centre	No. patients	Centre	No. patients
Ancona	15	Berlin	47
Ljubljana	12	Brisbane	45
Padua	7	Kyoto	40
Prague	9	Ljubljana	44
Santiago	23	Munich	101
Sofia	21	Sendai	63
Thessaloniki	36	Torino	80
Torino	23	Warsaw	30
Trieste	13	Yokohama City	76
Udine	53		
Warsaw	4		
Würzburg	19		
Total =	**235**	**Total =**	**526**

Table S2. Characteristics of patients with CT-management stratified for clinical outcome

VARIABLE	N	ALL	CLINICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
Clinical Outcome	235	233	90 (38.6)	113 (48.5)	30 (12.9)	N.A.
Age at surgery (years)	233	49 ± 11.3	45 ± 11.0	52 ± 10.6	51 ± 10.5	< 0.001
Gender (Female; %)	233	130 (55.8)	68 (75.6)	45 (39.8)	17 (56.7)	< 0.001
BMI (kg/m^2)	233	27.3 ± 4.4	26.0 ± 4.4	27.8 ± 4.1	28.9 ± 4.3	0.001
BASELINE PARAMETERS						
Aldosterone (pmol/L)	233	918.2 [632.5-1470.0]	921.0 [650.5-1735.8]	901.6 [622.8-1418.5]	918.2 [611.0-1326.7]	0.641
PRA (pmol/L/min)	145	2.6 [2.5-4.4]	2.6 [2.4-3.8]	2.6 [2.6-5.2]	2.8 [1.9-4.7]	0.314
ARR_PRA	145	413.6 [216.9-835.7]	479.1 [222.5-1069.6]	334.9 [172.6-752.8]	355.6 [189.3-713.8]	0.235
DRC (mU/L)	88	2.5 [2.5-3.8]	2.5 [1.8-2.6]	2.5 [2.5-4.8]	3.5 [1.9-5.4]	0.100
ARR_DRC	88	264.1 [181.4-381.4]	313.6 [251.5-432.9]	223.0 [172.1-340.4]	203.4 [125.2-357.0]	0.041
Lowest serum potassium (mmol/L)	233	3.2 ± 0.7	3.1 ± 0.6	3.2 ± 0.7	3.3 ± 0.8	0.473
Systolic BP (mmHg)	233	159 ± 18.9	157 ± 18.0	161 ± 19.1	158 ± 20.4	0.386
Diastolic BP (mmHg)	232	99 ± 11.9	99 ± 11.1	99 ± 12.5	96 ± 11.8	0.377
Anti-hypertensive medication (DDD)	232	2.7 [1.7-4.3]	2.0 [1.0-3.3]	3.3 [2.3-5.0]	2.3 [1.3-3.5]	< 0.001
Diabetes (yes; %)	232	29 (12.5)	9 (10.0)	13 (11.6)	7 (23.3)	0.148
eGFR ($mL/min/m^2$)	208	94 ± 24.5	99 ± 21.4	90 ± 26.2	88 ± 24.8	0.029
Albuminuria (mg/day)	129	15 [10.0-63.5]	16 [10.0-90.5]	16 [10.0-44.3]	10.0 [10.0-27.6]	0.689
LVH-Echocardiography (yes; %)	181	88 (48.6)	26 (37.7)	52 (57.1)	10 (47.6)	0.051

VARIABLE	N	ALL	CLINICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
Largest nodule at imaging (diameter, mm)	233	16 [11.0-22.0]	18 [12.0-26.3]	15 [10.0-20.0]	16 [9.8-20.0]	0.022
FOLLOW-UP PARAMETERS						
Aldosterone (pmol/L)	232	273.3 [141.5-438.3]	191.6 [117.6-388.8]	277.4 [148.4-441.7]	438.3 [304.9769.4]	< 0.001
PRA (pmol/L/min)	136	11.7 [5.7-25.6]	12.8 [8.7-26.8]	12.8 [7.2-26.8]	4.5 [3.6-9.0]	< 0.001
ARR _PRA	136	15.1 [7.8-45.1]	11.4 [5.5-26.0]	15.8 [7.6-38.6]	107.1 [64.5-213.5]	< 0.001
DRC (mU/L)	94	11.2 [7.0-11.2]	10.5 [7.0-21.7]	11.2 [9.2-20.4]	9.6 [5.7-24.9]	0.769
ARR_DRC	94	28.6 [16.9-44.2]	28.9 [18.3-49.5]	27.7 [16.4-40.5]	34.8 [10.2-84.9]	0.543
Lowest serum potassium (mmol/L)	232	4.3 ± 0.5	4.4 ± 0.4	4.4 ± 0.5	4.2 ± 0.5	0.130
Systolic BP (mmHg)	233	133 ± 13.9	125 ± 9.6	136 ± 11.8	150 ± 13.8	< 0.001
Diastolic BP (mmHg)	233	83 ± 8.9	79 ± 6.1	85 ± 8.0	92 ± 10.5	< 0.001
Anti-hypertensive medication (DDD)	233	1.0 [0.0-2.0]	0.0 [0.0-0.0]	1.6 [1.0-2.2]	3.2 [1.5-5.3]	< 0.001
POST-OPERATIVE CHANGE (BASELINE –FOLLOW UP)						
Δ-Aldosterone (%)	232	0.70 [0.46-0.88]	0.78 [0.55-0.91]	0.67 [0.47-0.86]	0.41 [0.13-73]	< 0.001
Δ-SBP (mmHg)	233	26 ± 18.4	32 ± 16.5	25 ± 17.4	9 ± 16.0	< 0.001
Δ-DBP (mmHg)	232	16 ± 12.2	21 ± 11.2	15 ± 11.6	4 ± 7.8	< 0.001
Δ-DDD	232	1.5 [0.7-2.5]	2.0 [1.0-3.3]	1.5 [1.0-2.5]	-0.5 [-2.2-0.1]	< 0.001

The Δ post-operative changes are calculated as baseline minus follow-up as indicted. A positive value indicates a decrease and a negative value indicates an increase. Therefore a negative value for the delta-DDD has to be considered as a rise in medication and not a fall. BMI, body mass index; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; ARR_PRA, ARR calculated using PRA; DRC, direct renin concentration; ARR_DRC, ARR calculated using direct renin concentration; BP, blood pressure; DDD, defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/); eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy.

Table S3. Characteristics of patients with CT-management stratified for biochemical outcome

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
Biochemical Outcome	235	235	188 (80.0)	18 (7.7)	29 (12.3)	N.A.
Age at surgery (years)	235	49 ± 11.3	49 ± 11.6	52 ± 12.0	52 ± 8.5	0.230
Gender (Female; %)	235	132 (56.2)	111 (59.0)	9 (50.0)	12 (41.4)	0.175
BMI (kg/m^2)	235	27.2 ± 4.4	26.8 ± 4.4	28.9 ± 4.1	28.9 ± 3.5	0.011
BASELINE PARAMETERS						
Aldosterone (pmol/L)	235	923.7 [635.2-1481.3]	1022.0 [631.8-1586.8]	891.9 [697.7-1129.8]	813.0 [518.8-1050.0]	0.108
PRA (pmol/L/min)	147	2.6 [2.6-4.4]	2.6 [2.6-4.1]	3.8 [2.6-7.2]	2.6 [2.1-4.8]	0.383
ARR_PRA	147	419.4 [217.0-835.9]	506.3 [222.5-933.0]	267.0 [159.3-413.6]	315.8 [155.8-682.0]	0.090
DRC (mU/L)	88	2.5 [2.5-3.8]	2.5 [2.5-3.4]	2.5 [2.2-6.7]	4.7 [2.5-7.0]	0.290
ARR_DRC	88	264.1 [181.4-381.4]	269.1 [188.5-413.0]	274.1 [115.6-345.1]	160.5 [108.5-291.8]	0.177
Lowest serum potassium (mmol/L)	234	3.2 ± 0.7	3.1 ± 0.7	3.4 ± 0.7	3.4 ± 0.6	0.041
Systolic BP (mmHg)	234	159 ± 18.8	159 ± 18.9	152 ± 11.8	165 ± 20.6	0.068
Diastolic BP (mmHg)	233	99 ± 11.9	99 ± 12.0	96 ± 8.4	93 ± 29.4	0.097
Anti-hypertensive medication (DDD)	232	2.7 [1.7-4.3]	2.5 [1.5-4.3]	2.7 [1.8-3.5]	3.3 [2.0-4.9]	0.371
Diabetes (yes; %)	234	29 (12.4)	19 (10.1)	3 (17.6)	7 (24.1)	0.081
eGFR (mL/min/m^2)	209	94 ± 24.5	94 ± 24.1	91 ± 21.4	93 ± 29.4	0.898
Albuminuria (mg/day)	130	15 [10.0-62.8]	16 [10.0-65.0]	10 [10.0-14.0]	17 [10.0-81.5]	0.309
LVH-Echocardiography (yes; %)	182	88 (48.4)	64 (44.8)	11 (68.8)	13 (56.5)	0.134
Largest nodule at imaging (diameter, mm)	235	16 [11.0-22.0]	17 [12.0-22.8]	13 [8.8-16.3]	15 [9.5-20.0]	0.051

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
FOLLOW-UP PARAMETERS						
Aldosterone (pmol/L)	234	273.3 [141.5-438.3]	216.4 [122.1-368.2]	442.5 [305.9-617.2]	498.0 [413.3-774.6]	< 0.001
PRA (pmol/L/min)	136	11.7 [5.7-25.6]	14.1 [8.8-27.1]	5.9 [4.2-17.9]	3.8 [2.6-7.9]	< 0.001
ARR_PRA	136	15.1 [7.8-45.1]	11.5 [5.9-19.7]	65.0 [45.5-105.7]	112.0 [77.8-326.1]	< 0.001
DRC (mU/L)	96	11.2 [7.2-21.9]	13.4 [9.3-23.4]	5.7 [3.9-7.1]	6.2 [2.1-6.8]	< 0.001
ARR_DRC	96	28.1 [16.6-42.9]	23.2 [14.2-33.9]	63.3 [57.8-65.7]	80.8 [74.3-178.3]	< 0.001
Lowest serum potassium (mmol/L)	234	4.3 ± 0.5	4.4 ± 0.5	4.3 ± 0.4	4.0 ± 0.5	< 0.001
Systolic BP (mmHg)	235	133 ± 13.8	130 ± 12.4	140 ± 11.1	147 ± 15.1	< 0.001
Diastolic BP (mmHg)	235	83 ± 8.9	82 ± 7.8	89 ± 8.1	91 ± 10.9	< 0.001
Anti-hypertensive medication (DDD)	235	1.0 [0.0-2.0]	0.7 [0.0-1.8]	1.8 [0.8-3.5]	2.3 [1.2-5.0]	< 0.001
POST-OPERATIVE CHANGE (BASELINE –FOLLOW UP)						
Δ-Aldosterone (%)	234	0.71 [0.47-0.88]	0.77 [0.54-0.91]	0.51 [0.21-0.67]	0.18 [-0.01-0.48]	< 0.001
Δ-SBP (mmHg)	234	26 ± 18.3	28 ± 17.8	12 ± 11.6	18 ± 20.0	< 0.001
Δ-DBP (mmHg)	233	16 ± 12.3	17 ± 12.1	7 ± 9.0	12 ± 12.3	0.001
Δ-DDD	232	1.5 [0.7-2.5]	1.5 [0.8-3.0]	1.0 [0.0-2.0]	1.0 [-1.0-2.1]	0.001

The Δ post-operative changes are calculated as baseline minus follow-up as indicted. A positive value indicates a decrease and a negative value indicates an increase. BMI, body mass index; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; ARR_PRA, ARR calculated using PRA; DRC, direct renin concentration; ARR_DRC, ARR calculated using direct renin concentration; BP, blood pressure; DDD, defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/); eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy.

Table S4. Characteristics of patients with AVS-management stratified for clinical outcome

VARIABLE	N	ALL	CLINICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
Clinical Outcome	526	526	196 (37.3)	250 (47.5)	80 (15.2)	N.A.
Age at surgery (years)	526	51 ± 11.0	46 ± 10.6	53 ± 10.7	55 ± 9.5	< 0.001
Gender (Female; %)	526	245 (46.6)	133 (67.9)	91 (36.4)	21 (26.3)	< 0.001
BMI (kg/m^2)	526	27.1 ± 5.1	25.6 ± 5.2	27.8 ± 4.5	28.5 ± 5.8	< 0.001
BASELINE PARAMETERS						
Aldosterone (pmol/L)	525	876.6 [569.4-1439.7]	971.0 [618.7-1536.8]	868.3 [574.2-1406.8]	651.9 [452.2-1351.6]	0.002
PRA (pmol/L/min)	313	2.6 [1.3-5.1]	2.6 [1.3-5.1]	2.6 [1.3-5.1]	3.8 [1.3-6.4]	0.113
ARR_PRA	313	363.3 [158.3-708.7]	424.8 [174.2-829.5]	340.2 [159.0-661.0]	182.0 [95.9-406.9]	0.006
DRC (mU/L)	213	4.9 [3.2-10.1]	4.0 [2.0-6.0]	4.7 [3.2-10.6]	8.8 [4.1-15.3]	< 0.001
ARR_DRC	213	153.6 [60.2-297.2]	209.6 [119.7-364.3]	169.6 [50.0-294.9]	75.5 [37.8-146.7]	< 0.001
Lowest serum potassium (mmol/L)	526	3.1 ± 0.6	3.0 ± 0.6	3.1 ± 0.5	3.2 ± 0.5	0.005
Systolic BP (mmHg)	526	152 ± 22.2	147 ± 19.3	158 ± 23.8	147 ± 19.6	< 0.001
Diastolic BP (mmHg)	526	93 ± 13.6	91 ± 12.6	95 ± 13.7	88 ± 14.5	< 0.001
Anti-hypertensive medication (DDD)	526	2.7 [1.5-4.5]	2.0 [1.0-3.0]	3.7 [2.1-5.5]	3.0 [1.9-4.0]	< 0.001
Diabetes (yes; %)	526	78 (14.8)	13 (6.6)	45 (18.0)	20 (25.0)	< 0.001
eGFR (mL/min/m^2)	505	84 ± 22.0	91 ± 21.1	81 ± 21.7	78 ± 21.3	< 0.001
Albuminuria (mg/day)	415	15 [9.0-49.3]	11 [7.0-30.0]	21 [10.0-62.0]	25 [9.7-62.5]	< 0.001
LVH-Echocardiography (yes; %)	433	228 (52.7)	61 (37.4)	126 (63.0)	41 (58.6)	< 0.001
Largest nodule at imaging (diameter, mm)	526	13 [8.8-17.0]	15 [10.0-18.0]	12 [8.0-17.0]	13 [0.0-16.0]	0.007

VARIABLE	N	ALL	CLINICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
FOLLOW-UP PARAMETERS						
Aldosterone (pmol/L)	526	238.6 [140.0-338.4]	230.2 [135.9-330.8]	223.3 [135.2-316.2]	277.4 [181.0-382.1]	0.017
PRA (pmol/L/min)	303	19.2 [6.9-38.4]	17.9 [7.0-29.8]	23.0 [6.5-39.7]	17.9 [8.6-42.9]	0.781
ARR_PRA	303	13.2 [5.4-31.0]	15.1 [6.0-32.5]	10.5 [4.7-31.0]	17.3 [5-7-29.0]	0.782
DRC (mU/L)	223	22.4 [11.0-36.2]	21.3 [11.0-32.2]	23.0 [11.2-33.3]	23.0 [9.4-46.8]	0.642
ARR_DRC	223	9.4 [4.5-18.7]	8.8 [5.2-14.7]	9.9 [4.1-17.6]	11.1 [4.2-27.5]	0.486
Lowest serum potassium (mmol/L)	526	4.4 ± 0.4	4.4 ± 0.4	4.5 ± 0.5	4.2 ± 0.4	< 0.001
Systolic BP (mmHg)	526	129 ± 14.3	121 ± 0.4	133 ± 13.0	138 ± 17.1	< 0.001
Diastolic BP (mmHg)	526	81 ± 10.3	76 ± 7.5	84 ± 10.1	87 ± 11.7	< 0.001
Anti-hypertensive medication (DDD)	526	0.5 [0.0-2.3]	0.0 [0.0-0.0]	1.3 [0.5-3.0]	3.0 [1.5-5.2]	< 0.001
POST-OPERATIVE CHANGE (BASELINE –FOLLOW UP)						
Δ-Aldosterone (%)	525	0.75 [0.53-0.87]	0.79 [0.60-0.88]	0.76 [0.54-0.88]	0.57 [0.32-0.80]	< 0.001
Δ-SBP (mmHg)	526	23 ± 22.4	27 ± 19.9	25 ± 22.6	9 ± 22.0	< 0.001
Δ-DBP (mmHg)	526	11 ± 14.2	15 ± 12.2	12 ± 13.5	1 ± 16.2	< 0.001
Δ-DDD	526	1.5 [0.5-3.0]	2.0 [1.0-3.0]	2.0 [0.9-3.3]	-0.8 [-1.6-0.5]	< 0.001

The Δ post-operative changes are calculated as baseline minus follow-up as indicted. A positive value indicates a decrease and a negative value indicates an increase. BMI, body mass index; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; ARR_PRA, ARR calculated using PRA; DRC, direct renin concentration; ARR_DRC, ARR calculated using direct renin concentration; BP, blood pressure; DDD, defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/); eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy.

Table S5. Characteristics of patients with AVS-management stratified for biochemical outcome

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
Biochemical Outcome	526	526	491 (93.3)	25 (4.8)	10 (1.9)	N.A.
Age at surgery (years)	526	51 ± 11.1	51 ± 11.0	52 ± 10.0	49 ± 14.1	0.787
Gender (Female; %)	526	245 (46.6)	229 (46.6)	12 (48.0)	4 (40.0)	0.907
BMI (kg/m^2)	526	27.1 ± 5.1	27.1 ± 5.0	25.8 ± 5.4	30.3 ± 6.7	0.062
BASELINE PARAMETERS						
Aldosterone (pmol/L)	525	876.6 [569.4-1439.7]	886.3 [571.1-1445.3]	768.4 [575.6-1532.6]	550.6 [407.1-948.0]	0.112
PRA (pmol/L/min)	313	2.6 [1.3-5.1]	2.6 [1.3-5.1]	2.6 [1.3-5.1]	3.8 [2.6-3.8]	0.768
ARR_PRA	313	363.3 [158.3-708.7]	364.6 [159.4-686.8]	257.0 [141.4-877.2]	129.3 [114.9-129.3]	0.550
DRC (mU/L)	213	4.9 [3.2-10.1]	4.7 [3.2-10.0]	11.5 [4.7-15.3]	6.6 [3.2-17.2]	0.329
ARR_DRC	213	153.6 [60.2-297.2]	160.1 [68.6-305.6]	63.8 [29.9-192.9]	89.0 [29.6-181.6]	0.131
Lowest serum potassium (mmol/L)	526	3.1 ± 0.6	3.1 ± 0.6	3.3 ± 0.5	3.1 ± 0.6	0.199
Systolic BP (mmHg)	526	152 ± 22.2	153 ± 22.2	142 ± 21.2	142 ± 13.4	0.018
Diastolic BP (mmHg)	526	93 ± 13.6	93 ± 13.5	87 ± 14.6	91 ± 12.9	0.070
Anti-hypertensive medication (DDD)	526	2.7 [1.5-4.5]	2.7 [1.5-4.5]	2.3 [1.8-3.4]	4.3 [2.8-6.1]	0.244
Diabetes (yes; %)	526	78 (14.8)	73 (14.9)	3 (12.0)	2 (20.0)	0.831
eGFR (mL/min/m^2)	505	84 ± 22.0	84 ± 21.8	90 ± 23.0	80 ± 30.8	0.307
24 h Albuminuria (mg/day)	415	15.0 [9.0-49.3]	15.0 [9.0-49.2]	10.6 [5.5-33.9]	61.0 [13.5-464.7]	0.034
LVH-Echocardiography (yes; %)	433	228 (52.7)	216 (53.2)	8 (44.4)	4 (44.4)	0.677
Largest nodule at imaging (diameter, mm)	526	13 [8.8-17.0]	13 [9.0-18.0]	12 [7.0-15.0]	13 [0.0-16.0]	0.240

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
FOLLOW-UP PARAMETERS						
Aldosterone (pmol/L)	526	238.6 [140.0-338.4]	227.5 [138.7-324.6]	316.2 [223.3-418.9]	427.2 [278.8-790.6]	< 0.001
PRA (pmol/L/min)	303	19.2 [6.9-38.4]	23.0 [9.0-39.7]	2.6 [1.3-5.1]	3.8 [2.6-3.8]	< 0.001
ARR_PRA	303	13.3 [5.4-31.0]	10.8 [5.1-25.6]	71.5 [44.3-142.0]	74.4 [53.3-74.4]	< 0.001
DRC (mU/L)	223	22.4 [11.0-36.2]	23.0 [11.3-37.5]	6.2 [2.6-7.2]	13.0 [8.5-22.0]	0.003
ARR_DRC	223	9.5 [4.5-18.7]	9.0 [4.4-16.4]	65.5 [53.5-79.2]	28.9 [19.9-115.1]	< 0.001
Lowest serum potassium (mmol/L)	526	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	3.9 ± 0.5	0.001
Systolic BP (mmHg)	526	129 ± 14.3	129 ± 14.2	133 ± 17.1	136 ± 6.9	0.102
Diastolic BP (mmHg)	526	81 ± 10.3	81 ± 10.1	84 ± 13.5	84 ± 8.0	0.286
Anti-hypertensive medication (DDD)	526	0.5 [0.0-2.3]	0.5 [0.0-2.0]	0.7 [0.3-2.0]	3.6 [0.9-5.1]	0.009
POST-OPERATIVE CHANGE (BASELINE –FOLLOW UP)						
Δ-Aldosterone (%)	525	0.75 [0.53-0.87]	0.76 [0.55-0.88]	0.58 [0.44-0.85]	0.20 [-0.06-0.38]	< 0.001
Δ-SBP (mmHg)	526	23 ± 22.4	24 ± 22.2	9 ± 20.9	6 ± 16.5	< 0.001
Δ-DBP (mmHg)	526	11 ± 14.2	12 ± 13.9	3 ± 17.5	7 ± 9.8	0.004
Δ-DDD	526	1.5 [0.5-3.0]	1.5 [0.5-3.0]	1.3 [0.5-2.3]	0.8 [-2.1-4.8]	0.378

The Δ post-operative changes are calculated as baseline minus follow-up as indicted. A positive value indicates a decrease and a negative value indicates an increase. BMI, body mass index; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; ARR_PRA, ARR calculated using PRA; DRC, direct renin concentration; ARR_DRC, ARR calculated using direct renin concentration; BP, blood pressure; DDD, defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/); eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy.

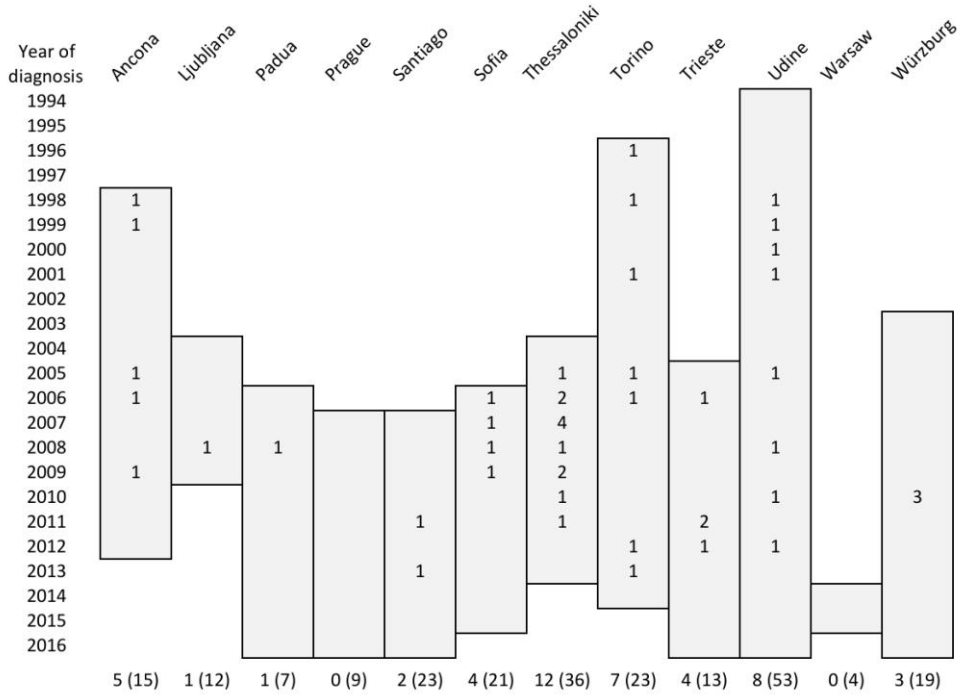

Figure S1. Timeline of absent and partial biochemical outcomes of patients with CT-based surgical decision.

The vertical columns show the period of patient inclusion (year-year) of each centre (shown at the top) with the numbers of patients with absent or partial biochemical success shown within each bar with the corresponding year on the left. For each centre, the total number of patients with an absent or partial biochemical outcome (persisting aldosteronism) is shown at the bottom of each column with the total number of patients included in the study shown in parenthesis.

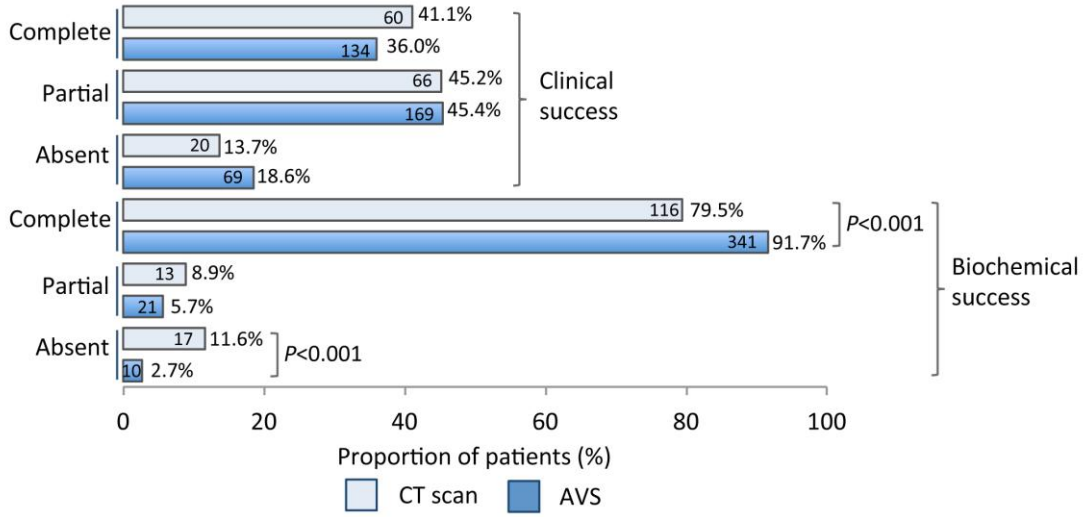

Figure S2. Subanalysis of clinical and biochemical outcomes of patients stratified by surgical management decision

Clinical and biochemical outcomes was assessed in centres performing only CT or AVS-based management. Absolute numbers are shown in parenthesis for each clinical or biochemical outcome category (complete, partial or absent). A total of 146 and 372 patients had clinical and biochemical outcome data in the CT scan group and the AVS groups, respectively. The outcomes are similar to the analysis of the total cohort (Figure 1).

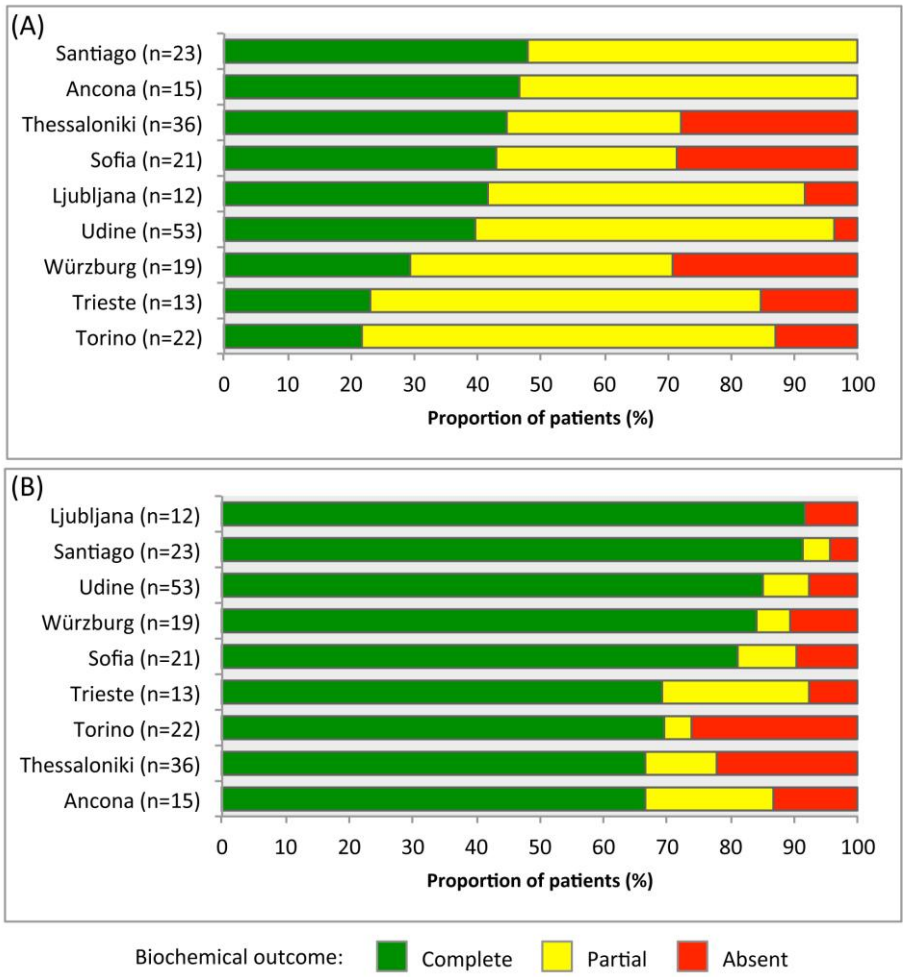

Figure S3. Clinical and biochemical outcomes of patients treated by adrenalectomy for unilateral primary aldosteronism with CT-based management.

Clinical (A) and biochemical (B) outcomes are shown in centres with study cohorts of more than 10 patients.