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Abstract

Unilateral primary aldosteronism is the most common surgically correctable form of endocrine hypertension and is usually differentiated from bilateral forms by adrenal venous sampling or computed tomography. Our objective was to compare clinical and biochemical post-surgical outcomes of patients with unilateral primary aldosteronism diagnosed by computed tomography or adrenal venous sampling and identify predictors of surgical outcomes. Patient data were obtained from 18 internationally distributed centres and retrospectively analysed for clinical and biochemical outcomes of adrenalectomy of patients with surgical management based on computed tomography (n=235 patients, diagnosed from 1994 to 2016) or adrenal venous sampling (526 patients, diagnosed from 1994 to 2015) using the standardised Primary Aldosteronism Surgical Outcome criteria. Biochemical outcomes were highly different according to surgical management approach with a smaller proportion in the computed tomography group achieving complete biochemical success (188 of 235 [80%] patients *versus* 491 of 526 [93%], p<0.001) and a greater proportion with absent biochemical success (29 of 235 [12%] *versus* 10 of 526 [2%], p<0.001). A diagnosis by computed tomography was associated with a decreased likelihood of complete biochemical success compared with adrenal venous sampling (OR 0.28, 0.16-0.50; p<0.001). Clinical outcomes were not significantly different but the absence of a post-surgical elevated aldosterone-to-renin ratio was a strong marker of complete clinical success (OR 14.81, 1.76-124.53; p=0.013) in the computed tomography but not in the adrenal venous sampling group. In conclusion, patients diagnosed by computed tomography

have a decreased likelihood of achieving complete biochemical success compared with a diagnosis by adrenal venous sampling.

Key words

Primary aldosteronism, adrenal venous sampling, aldosterone producing adenoma, bilateral adrenal hyperplasia, adrenalectomy, endocrine hypertension

Introduction

Primary aldosteronism (PA) is a frequent cause of secondary hypertension with a reported prevalence of 5-10% in unselected populations and up to 20% in patients with resistant hypertension.[1-5] The excess aldosterone production that causes the disorder may be unilateral (confined to one adrenal) or bilateral and the two forms are preferentially treated by unilateral adrenalectomy or a mineralocorticoid receptor antagonist, respectively.[6, 7] Unilateral PA is the most common surgically correctable cause of hypertension with a highly variable proportion of patients achieving clinical remission after surgery between centres.[8-10]

Patients with PA have a widely reported increased risk of prevalent cardiovascular and cerebrovascular complications and target organ damage relative to matched patients with primary hypertension who have otherwise similar cardiovascular risk profiles or compared with the general population with hypertension.[11-17] An increasing body of evidence implies that an early diagnosis and targeted treatment can minimise or reverse the increased risks associated with this condition. Failure to identify those with unilateral forms constrains patients with unilateral disease to a lifetime of medical treatment instead of offering a potential surgical cure and has an impact on quality of life.[18-21]

The accurate differention of unilateral from bilateral PA is therefore mandatory for optimal clinical management and is widely undertaken by adrenal venous sampling (AVS) and/or an imaging technique, usually adrenal computed tomography (CT) or magnetic resonance. AVS determines whether one or both

adrenals are responsible for aldosterone excess. The ability of AVS to provide functional information regarding the source of aldosterone overproduction in PA might be expected to render it superior in terms of diagnostic accuracy than imaging techniques such as CT which provide only structural information. Indeed, CT has been widely reported to be unreliable for differentiation of unilateral from bilateral PA, lacks sensitivity for the detection of microadenomas (<10 mm diameter) and specificity in patients with non-functional adrenal incidentalomas.[6, 22-27] For these reasons AVS is recommended for the diagnostic work up of PA by the clinical practice guideline of the Endocrine Society.[6] The only randomised prospective clinical trial that compared AVS and CT in the differentiation of unilateral from bilateral PA found no significant differences in clinical outcomes between the two approaches. A non-significant difference in biochemical outcomes (80% biochemical remission in the CT *versus* 89% in the AVS group) and health-related quality of life was also reported and the study concluded that the reference standard status of AVS in the diagnostic work up of PA was unjustified.[28]

Our objective was to evaluate the diagnostic value of CT compared with AVS for unilateral PA in a large international cohort of patients retrospectively assessed for clinical and biochemical outcomes by the international primary aldosteronism surgical outcome (PASO) consensus[10] and to identify predictors of outcomes.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

An expanded Methods section is available in the online-only data supplement

Patient cohorts and outcome assessment

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). Data from 761 patients with unilateral PA were obtained (235 with CT management diagnosed from 1994 to 2016, and 526 with AVS management diagnosed from 1994 to 2015) (Table S1, Figure S1). The patients in the AVS group are a subset of the patients from the PASO study with the addition of CT data and 4 extra patients (2 in Munich and 2 in Berlin) due to newly available outcome data. 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 PA was diagnosed if a unilateral nodule of at least 8 mm in diameter was detected. Clinical and biochemical outcomes were assessed retrospectively in accordance with the standardised criteria of the PASO consensus with follow-up at 6-12 months which are based on blood pressure measurements and antihypertensive drug dosage (clinical outcomes) and assessment of the aldosterone-to-renin ratio and normalisation of hypokalemia (if present pre-surgically) (biochemical outcomes).[10] PA was diagnosed by the US Endocrine Society guideline or the Japan Endocrine Society guideline.[6, 29] All details on patient inclusion and assessment are provided in the online-only data supplement. The study was

approved by an institutional review board with patient data and written informed patient consent obtained in accordance with local ethical guidelines.

Statistical analyses

Data are expressed as absolute numbers and percentages, means with standard deviations (SD) or as medians with interquartile ranges (IQR) as appropriate. IBM SPSS statistics version 22.0 was used for all analyses. P values <0.05 were considered significant. Details of all statistics are given in the online-only data supplement.

Results

An expanded Results section is available in the online-only data supplement

Biochemical outcomes stratified by CT and AVS based surgical decision

The CT group comprised a smaller proportion of patients achieving complete biochemical success after surgery (cure of PA) (188 of 235 patients, 80.0%) compared with AVS (491 of 526, 93.3%) (p<0.001) and a higher proportion with absent biochemical success (12.3% *versus* 1.9%, p<0.001) and persisting PA (partial and absent biochemical success combined) (20.0% *versus* 6.7%, p<0.001) (Figure 1 and Table 1). Similar clinical and biochemical outcomes were observed when the analysis was restricted to centres using either an AVS or CT scan approach (Figure S2).

Clinical outcomes stratified by CT and AVS based surgical decision

The proportion of patients achieving complete clinical success was similar (38.6% *versus* 37.3% in the CT and AVS groups, respectively, p=0.718) (Figure 1,

Table 1). Despite this, in the CT group, the median post-surgical aldosterone-to-renin ratio (measured with plasma renin activity [PRA] because direct renin concentration measurements may perform less well compared with PRA for low renin values)[30, 31] was highly elevated in patients with an absent clinical outcome [107.1, IQR 64.5-213.5] (Table S2) and significantly greater than in patients with either partial ($p<0.001$) or complete clinical success ($p<0.001$) (Figure 2, Table S2). Patients with AVS management displayed no significant differences in the aldosterone-to-renin ratio stratified for clinical outcomes (Figure 2, Table S4).

Assessment of post-surgical outcomes across centres indicated less variance in clinical remission (22-48%) and a wider variance in biochemical remission (67-92%) with CT managment relative to that noted previously with AVS (Figure S2).[10] There was no discernable timeline bias for the diagnosis of the patients with absent or partial biochemical success with CT surgical management (Figure S1) and these patients were not concentrated in any particular centre (Figure S3).

Identification of factors associated with CT and AVS based surgical outcomes

Patient characteristics were stratified for clinical and biochemical outcomes based on CT- (Tables S2 and S3) or AVS-based management (Tables S4 and S5). In agreement with the PASO study, the unadjusted analysis showed that younger age, female sex, lower body mass index (BMI) and an absence of target organ damage to kidneys and heart were factors associated with complete clinical success in the AVS group (Table S4). Three of these (younger age, female sex and

lower BMI) were also associated with complete clinical success in the CT group (Table S2).

A CT-based surgical decision was a factor associated with a lower likelihood of complete biochemical success compared with an AVS-based surgical decision (complete *versus* partial + absent: adjusted OR 0.28, 0.16-0.50; p<0.001). The approach to surgical management did not influence the likelihood clinical outcomes (Table 2).

In the total cohort the absence of an elevated aldosterone-to-renin ratio at follow-up was a factor associated with both complete clinical success (adjusted OR 4.92, 1.63-14.88; p=0.005) and clinical benefit (complete + partial clinical success combined: adjusted OR 7.46, 3.35-16.63; p<0.001) (Table 2). This marker of clinical outcome was driven by patients with CT management where the absence of an elevated post-surgical aldosterone-to-renin ratio was associated with complete clinical outcome (adjusted OR 14.81, 1.76-124.53; p=0.013) and clinical benefit (adjusted OR 45.49, 11.63-177.93; p<0.001). The aldosterone-to-renin ratio at follow-up was not associated with clinical outcome in the AVS group (Table 2).

Reliability of CT compared with AVS for the diagnosis of unilateral primary aldosteronism including young patients below 35 years of age

In the diagnostic work up of PA, CT scanning precedes AVS to exclude the presence of an adrenocortical carcinoma. Comparison of CT with AVS results showed discordant findings in 178 (36% of 491) patients with AVS management

(who were biochemically cured after adrenalectomy). If CT data had been used for subtype differentiation, resection of the wrong adrenal would have occurred in 9 patients (2%) and 169 patients (34%) would have missed the chance of surgery because of an inappropriate diagnosis of bilateral disease (71 patients [14%] with bilateral normal and 98 patients [20%] with bilateral abnormal adrenals) (Figure 3A).

We tested the reliability of CT management in young patients (<35 years) with specific biochemical (baseline plasma aldosterone concentration >30 ng/dL and spontaneous hypokalemia) and imaging characteristics . There were 40 (7.6% of 526) and 20 (8.5% of 235) patients aged less than 35 years of age in the AVS and CT groups, respectively. The CT results indicated that 26 of the patients in the AVS group (65% of 40, all with complete biochemical success) and 11 in the CT group (55% of 20 patients, 8 complete, 1 partial and 2 absent biochemical success) had a unilateral adrenal mass (> 10 mm diameter) with a normal appearing contralateral adrenal. These imaging results combined with a marked phenotype of PA at baseline (plasma aldosterone concentration > 30 ng/dL and spontaneous hypokalemia) were observed in 17 (12 complete and 5 partial clinical success) and 5 (2 complete, 2 partial clinical success and 1 with missing clinical data) patients aged less than 35 years, all of whom were biochemically cured by adrenalectomy.

Discussion

The diagnosis of unilateral PA by AVS and treatment by total unilateral adrenalectomy results in biochemical remission in more than 9 out of 10

patients and clinical remission or a marked improvement in clinical parameters in just over 4 out of 5 patients.[10] An outcome of partial or absent biochemical success after surgery defines those patients with persisting hyperaldosteronism and therefore presumably bilateral PA that was misdiagnosed as unilateral pre-operatively . The accurate diagnosis of unilateral PA that determines the therapeutic strategy is thus fundamental if a patient is to be offered the possibility of biochemical cure.

Herein we show that the likelihood of cure of aldosteronism (complete biochemical success) with AVS-based surgical management is higher relative to surgery based on adrenal CT. Although this was not accompanied by a higher likelihood of clinical cure, it is noteworthy that evidence of persisting PA (indicated by an elevated aldosterone-to-renin ratio which is a criterion of absent and partial biochemical success) in patients with a CT-based diagnosis was associated with unfavourable clinical outcomes (absent in patients with AVS management). Furthermore, it is well established that long-term excessive and autonomous aldosterone production leads to severe detrimental effects independent of blood pressure control and carries an increased risk of cardiovascular and cardiometabolic events and death relative to patients with primary hypertension.[5, 11-16] Additionally, the persistence of low plasma renin activity levels in patients with PA treated with mineralocorticoid receptor antagonists (indicating persistence of inappropriate activation of the mineralocorticoid receptor by aldosterone) are associated with unfavourable cardiovascular long term outcomes.[16] These observations highlight the clinical importance of biochemical (and not just clinical) cure and support the

recommendation of long-term yearly follow-up with both clinical and biochemical assessment in adrenalectomized patients with PA .[10, 16] Herein we report that in the group with an AVS based surgical decision, the ARR was not elevated in patients with absent clinical outcomes indicating that other factors likely determined the lack of clinical remission such as pre-existing primary hypertension, long-duration of hypertension, older age and renal insufficiency. In contrast, with CT management, persistent hyperaldosteronism was a potential additional factor that contributed to absent clinical outcomes indicated by the elevated ARR.

The main differences between our study and that of Dekkers et al.,[28] other than the retrospective observational *versus* prospective randomised design, was the assessment of outcomes in accordance with a standardised set of criteria[10] and the greater number of patients with unilateral PA included in the present study (235 and 526 patients in the CT and AVS groups respectively) compared with the prospective study (46 patients in each group). Despite these differences, the proportions of patients with complete biochemical success reported in both are highly similar (80% with a diagnosis by CT in both studies and 93% *versus* 89%, in this and in Dekkers' study, diagnosed by AVS). These observations raise the possibility that with sufficient numbers the prospective SPARTACUS study would also have demonstrated significant differences in surgical outcomes between the CT- and AVS-based treatment groups, as acknowledged by Dekkers et al.[28]

The present study is the largest cohort to date that employs uniform (albeit post hoc) follow up data assessed in accordance with an international consensus.[10]

We demonstrate the lower performance of non-functional imaging compared with AVS for the diagnosis of lateralised aldosterone excess in unilateral PA. The high level of discordance between imaging and AVS results for determining lateralisation in PA has been reported previously.[25, 32] Our data also support the concept that adrenal CT may tend to miss smaller adenomas because the median size of the adenomas detected in the CT group was significantly larger than in the AVS group (determined by CT scanning).

In patients with confirmed unilateral PA (on the basis of biochemical cure at follow up) imaging data alone would result in 1 in every 50 patients undergoing the removal of the wrong adrenal and 1 in every 3 patients missing the chance of surgery and the possibility of a cure (by being misdiagnosed as bilateral normal or bilateral abnormal). A higher number of misdiagnoses could result if patients less than 35 years of age are excluded. The overall discordance between CT and AVS results we report is highly similar to that of a systematic review (36% *versus* 38%) albeit the incidence of potential adrenalectomies on the wrong side in our study is lower (2% *versus* 4%), a difference that may be accounted for by the availability of follow-up data in all patients in our study and the inclusion of only patients with confirmed PA.[25] Despite the high level of discordance, we show in a cohort of 60 young patients (aged below 35 years) that CT scanning combined with predictors based on young age and phenotype is a reliable approach to bypass AVS as recommended by the ES guideline[6] and in agreement with a study performed in Japan.[33]

Limitations include the retrospective design and the potential for selection bias, the use of criteria for lateralization by CT that were not rigidly defined and office blood pressure measurements that were standard practice during much of the study period of patient evaluation. This may help to explain why the major differences between the CT and AVS cohorts reported herein were not defined by blood pressure measurements but by biochemical parameters.

The strengths of our study are the large cohort with patient follow-up data from diverse international centres with outcomes assessed in accordance with an internationally recognised set of criteria developed by a group of experts in the field.

Perspectives

Compared with AVS, a diagnosis of unilateral PA by CT results in similar clinical outcomes (blood pressure and antihypertensive medication) but decreases the likelihood of biochemical cure following treatment by adrenalectomy. Based on our data, CT based decision making is a valid strategy in young patients with PA with a marked phenotype but otherwise AVS should be considered the preferred method to differentiate unilateral from bilateral PA. Notwithstanding, it should be acknowledged that AVS is a challenging and non-standardised technique that is not available at all centres. However, the correct diagnosis and treatment of patients with unilateral forms offers a potential cure and the possibility to avoid comorbidities associated with long-term inappropriate aldosterone production.

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Conflicts of Interests

None

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Novelty and Significance:

1) What is New?

- We assessed outcomes of 761 patients treated by total unilateral adrenalectomy for unilateral primary aldosteronism with a surgical approach based on CT or AVS

- CT based management was more likely to be associated with inappropriate post-surgical aldosterone production in patients with absent clinical success

- A diagnosis by CT was associated with a decreased likelihood of complete biochemical success compared with AVS

2) What is Relevant?

CT-based management predicts a decreased likelihood of biochemical cure of unilateral primary aldosteronism after surgery compared with AVS.

Summary

Patients with a diagnosis of unilateral primary aldosteronism by CT scanning have unfavourable biochemical outcomes compared with a diagnosis by AVS.

VARIABLE	N	TOTAL	SURGICAL MANAGEMENT		*P*-value
			CT	AVS	
Clinical Outcome (N = 759)	Complete	286 (37.7)	90 (38.6)	196 (37.3)	0.718
	Partial	363 (47.8)	113 (48.5)	250 (47.5)	0.806
	Absent	110 (14.5)	30 (12.9)	80 (15.2)	0.399
Biochemical Outcome (N = 761)	Complete	679 (89.2)	188 (80.0)	491 (93.3)	< 0.001
	Partial	43 (5.7)	18 (7.7)	25 (4.8)	0.109
	Absent	39 (5.1)	29 (12.3)	10 (1.9)	< 0.001
Age at surgery (years)	761	50.4 ± 11.1	49.3 ± 11.3	50.9 ± 11.0	0.068
Gender (Female; %)	761	377 (49.5)	132 (56.2)	245 (46.6)	0.014
BMI (kg/m^2)	761	27.1 ± 4.9	27.2 ± 4.4	27.1 ± 5.1	0.742
BASELINE PARAMETERS					
Aldosterone (pmol/L)	760	895.0 [590.9-1445.3]	923.7 [635.2-1481.3]	876.6 [569.4-1439.7]	0.056
PRA (pmol/L/min)	460	2.6 [1.3-5.1]	2.6 [2.6-4.4]	2.6 [1.3-5.1]	0.782
ARR_PRA	460	367.8 [170.2-748.7]	419.4 [217.0-835.9]	363.3 [158.3-708.7]	0.072
DRC (mU/L)	301	4.0 [2.5-7.9]	2.5 [2.5-3.8]	4.9 [3.2-10.1]	< 0.001
ARR_DRC	301	199.8 [91.6-324.6]	264.1 [181.4-381.4]	153.6 [60.2-297.2]	< 0.001
Lowest serum potassium (mmol/L)	760	3.1 ± 0.6	3.2 ± 0.7	3.1 ± 0.6	0.051
Systolic BP (mmHg)	760	154 ± 21.4	159 ± 18.8	152 ± 22.2	< 0.001
Diastolic BP (mmHg)	759	95 ± 13.4	99 ± 11.9	93 ± 13.6	< 0.001
Antihypertensive medication (DDD)	758	2.7 [1.5-4.5]	2.7 [1.7-4.3]	2.7 [1.5-4.5]	0.800
Diabetes (yes; %)	760	107 (14.1)	29 (12.4)	78 (14.8)	0.373
eGFR (mL/min/m^2)	714	87 ± 23.1	94 ± 24.5	84 ± 22.0	< 0.001
24 h Albuminuria (mg/day)	545	15.0 [9.9-50.0]	15.0 [10.0-62.8]	15.0 [9.0-49.3]	0.693

VARIABLE	N	TOTAL	SURGICAL MANAGEMENT		*P*-value
			CT	AVS	
LVH-Echocardiography (yes; %)	615	316 (51.4)	88 (48.4)	228 (52.7)	0.330
Largest nodule at imaging (diameter, mm)	761	14 [10.0-19.0]	16 [11.0-22.0]	13 [8.8-17.0]	< 0.001
FOLLOW-UP PARAMETERS					
Aldosterone (pmol/L)	760	241.3 [140.4-357.6]	273.3 [141.5-438.3]	238.6 [140.0-338.4]	0.020
PRA (pmol/L/min)	439	15.4 [6.4-30.7]	11.7 [5.7-25.6]	19.2 [6.9-38.4]	0.001
ARR_PRA	439	14.0 [5.9-33.6]	15.1 [7.8-45.1]	13.2 [5.4-31.0]	0.021
DRC (mU/L)	319	18.8 [9.3-30.8]	11.2 [7.2-21.9]	22.4 [11.0-36.2]	< 0.001
ARR_DRC	319	13.3 [5.7-26.4]	28.1 [16.6-42.9]	9.4 [4.5-18.7]	< 0.001
Lowest serum potassium (mmol/L)	760	4.4 ± 0.5	4.3 ± 0.5	4.4 ± 0.4	0.356
Systolic BP (mmHg)	761	130 ± 14.2	133 ± 13.8	129 ± 14.3	< 0.001
Diastolic BP (mmHg)	761	82 ± 9.9	83 ± 8.9	81 ± 10.3	0.013
Antihypertensive medication (DDD)	761	0.7 [0.0-2.0]	1.0 [0.0-2.0]	0.5 [0.0-2.3]	0.817
POST-OPERATIVE CHANGE (BASELINE – FOLLOW UP)					
Δ Systolic BP (mmHg)	760	24 ± 21.2	26 ± 18.3	23 ± 22.4	0.140
Δ Diastolic BP (mmHg)	759	13 ± 13.7	16 ± 12.3	11 ± 14.2	< 0.001
Δ DDD	758	1.5 [0.5-3.0]	1.5 [0.7-2.5]	1.5 [0.5-3.0]	0.508

Table 1. Clinical variables of patients stratified by CT or AVS based management

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.

Variables	Clinical outcome		Biochemical Outcome	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
CT GROUP: ***Complete vs. Partial + Absent (reference: Complete)***				
Age (per year)	0.96 (0.92-0.99)	0.024	0.99 (0.95-1.03)	0.652
Lowest serum potassium (per mmol/L)	1.39 (0.70-2.78)	0.347	2.27 (1.11-4.76)	0.024
BMI (per 1 Kg/m^2)	0.99 (0.91-1.08)	0.850	0.87 (0.79-0.96)	0.007
eGFR (per mL/min per 1.73m^2)	1.01 (0.99-1.02)	0.687	0.99 (0.98-1.01)	0.607
Sex (ref: female)	4.37 (2.02-9.46)	< 0.001	1.06 (0.47-2.39)	0.887
LVH (ref: not detected)	2.38 (1.12-5.06)	0.025	1.93 (0.87-4.30)	0.108
Elevated ARR at FU (ref: not detected)	14.81 (1.76-124.53)	0.013	N.A.	N.A.
CT GROUP: ***Complete + Partial vs. Absent (reference: Complete + Partial)***				
Age (per year)	1.04 (0.98-1.11)	0.216	1.00 (0.95-1.05)	0.989
Lowest serum potassium (per mmol/L)	1.61 (0.57-4.55)	0.370	3.23 (1.28-8.32)	0.013
BMI (per 1 Kg/m^2)	0.95 (0.81-1.12)	0.489	0.88 (0.78-0.99)	0.044
eGFR (per mL/min per 1.73m^2)	1.01 (0.98-1.03)	0.698	0.99 (0.98-1.02)	0.709
Sex (ref: female)	0.88 (0.24-3.18)	0.843	1.44 (0.52-3.99)	0.483
LVH (ref: not detected)	1.00 (0.28-3.60)	0.994	1.43 (0.53-3.82)	0.480
Elevated ARR at FU (ref: not detected)	45.49 (11.63-177.93)	< 0.001	N.A.	N.A.
AVS GROUP: ***Complete vs. Partial + Absent (reference: Complete)***				
Age (per year)	0.95 (0.93-0.98)	< 0.001	0.98 (0.94-1.02)	0.392
Lowest serum potassium (per mmol/L)	1.27 (0.85-1.85)	0.249	1.52 (0.75-3.03)	0.247
BMI (per 1 Kg/m^2)	0.96 (0.92-1.01)	0.097	0.96 (0.89-1.03)	0.218

eGFR (per mL/min per 1.73m^2)	1.01 (1.00-1.02)	0.071	0.99 (0.97-1.01)	0.330
Sex (ref: female)	2.48 (1.57-3.93)	< 0.001	0.93 (0.41-2.14)	0.873
LVH (ref: not detected)	1.98 (1.26-3.11)	0.003	0.63 (0.28-1.43)	0.269
Elevated ARR at FU (ref: not detected)	2.55 (0.68-9.59)	0.166	N.A.	N.A.
Basis for Surgery Decision (ref: CT scan)	N.A.	N.A.	N.A.	N.A.
AVS GROUP: ***Complete + Partial vs. Absent (reference: Complete + Partial)***				
Age (per year)	0.96 (0.93-0.99)	0.013	1.03 (0.96-1.11)	0.383
Lowest serum potassium (per mmol/L)	1.30 (0.79-2.17)	0.305	0.97 (0.30-3.13)	0.956
BMI (per 1 Kg/m^2)	0.94 (0.89-0.99)	0.016	0.89 (0.80-0.99)	0.038
eGFR (per mL/min per 1.73m^2)	1.01 (0.99-1.02)	0.427	1.02 (0.98-1.05)	0.352
Sex (ref: female)	2.15 (1.15-4.01)	0.016	1.76 (0.40-7.75)	0.455
LVH (ref: not detected)	0.95 (0.54-1.69)	0.864	0.62 (0.16-2.49)	0.501
Elevated ARR at FU (ref: not detected)	1.47 (0.39-5.58)	0.573	N.A.	N.A.
Basis for Surgery Decision (ref: CT scan)	N.A.	N.A.	N.A.	N.A.
AVS + CT GROUP: ***Complete vs. Partial + Absent (reference: Complete)***				
Age (per year)	0.96 (0.94-0.97)	< 0.001	0.99 (0.96-1.02)	0.400
Lowest serum potassium (per mmol/L)	1.28 (0.91-1.79)	0.157	1.82 (1.11-3.03)	0.018
BMI (per 1 Kg/m^2)	0.97 (0.93-1.01)	0.076	0.93 (0.88-0.98)	0.007
eGFR (per mL/min per 1.73m^2)	1.01 (0.99-1.02)	0.100	0.99 (0.98-1.01)	0.345
Sex (ref: female)	2.90 (1.96-4.27)	< 0.001	0.96 (0.55-1.69)	0.898
LVH (ref: not detected)	1.99 (1.36-2.91)	< 0.001	1.12 (0.64-1.95)	0.686
Elevated ARR at FU (ref: not detected)	4.92 (1.63-14.88)	0.005	N.A.	N.A.

Basis for Surgery Decision (ref: CT scan)	1.04 (0.67-1.60)	0.859	0.28 (0.16-0.50)	< 0.001
AVS + CT GROUP: ***Complete + Partial vs. Absent (reference: Complete + Partial)***				
Age (per year)	0.98 (0.95-1.01)	0.087	1.01 (0.97-1.05)	0.554
Lowest serum potassium (per mmol/L)	1.43 (0.92-2.22)	0.114	2.04 (1.02-4.17)	0.044
BMI (per 1 Kg/m^2)	0.93 (0.89-0.98)	0.005	0.88 (0.82-0.95)	0.002
eGFR (per mL/min per 1.73m^2)	1.01 (0.99-1.02)	0.319	1.01 (0.99-1.02)	0.747
Sex (ref: female)	1.81 (1.07-3.09)	0.028	1.50 (0.66-3.40)	0.327
LVH (ref: not detected)	0.94 (0.57.1.55)	0.802	1.01 (0.46-2.20)	0.999
Elevated ARR at FU (ref: not detected)	7.46 (3.35-16.63)	< 0.001	N.A.	N.A.
Basis for Surgery Decision (ref: CT scan)	1.85 (0.99-3.45)	0.053	0.15 (0.06-0.36)	< 0.001

Table 2. Clinical variables associated with outcomes stratified by CT- or AVS-based management decision.
Logistic regressions identified factors associated with complete clinical and biochemical success. An odds ratio greater than 1 shows an increased odds (or likelihood) of clinical or biochemical outcome whereas an odds ratio of less than 1 means that the odds for the indicated outcome are decreased. The odds ratios for serum potassium were calculated for lowest values and therefore an odds ratio greater than 1 indicates a decreased odds and an odds ratio less than 1 means that the odds are increased. BMI, body mass index; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; ARR at FU, aldoterone-to-renin ratio at follow-up (an elevated ARR was calculated by ARR_PRA > 65 or ARR_DRC > 102.6, with aldosterone in pmol/L, PRA in pmol/L/min and DRC mU/L); ref, reference; CT, computed tomography. NA, not applicable: an elevated ARR is a criterion of partial and absent biochemical success.

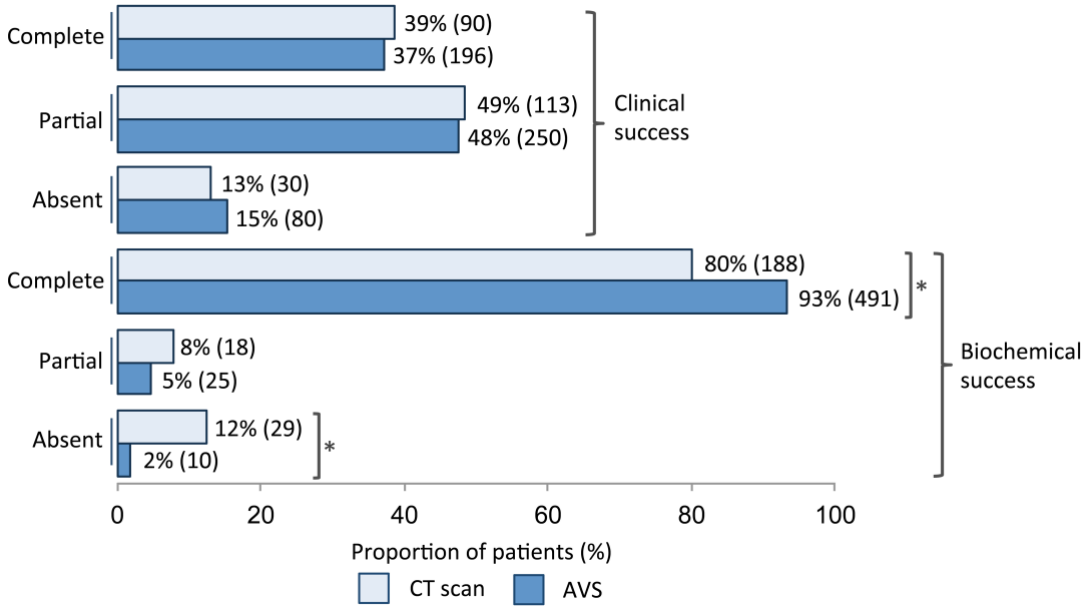

Figure 1. Clinical and biochemical outcomes of patients stratified by surgical management decision

Outcomes were assessed in accordance with the PASO consensus and are shown as proportions of patients (%) with absolute numbers in parenthesis for each clinical or biochemical outcome category (complete, partial or absent). A total of 233 and 235 patients had clinical and biochemical outcome data, respectively in the CT scan group and 526 patients had both clinical and biochemical outcome data in the AVS group. *p<0.001

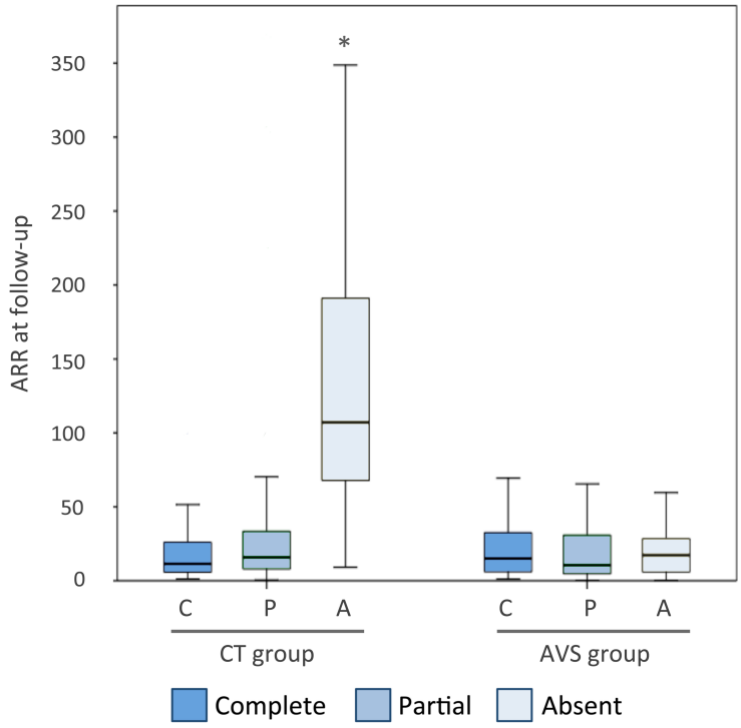

Figure 2. Stratification of the post-surgical aldosterone-to-renin ratio by clinical outcomes and surgical management decision

The box and whisker plot shows the median aldosterone-to-renin ratio at follow-up (thick horizontal line within bars) derived from plasma renin activities stratified for clinical outcomes (C, complete, P, partial, and A, absent clinical success) in the CT and AVS groups. The analysis included data from 136 patients in the CT group (complete [n=55], partial [n=61] and absent [n=20] success) and from 303 patients in the AVS group (complete [n=126], partial [n=147] and absent [n=30] success).

ARR, aldosterone-to-renin ratio assessed using the plasma renin activity; AVS, adrenal venous sampling; CT, computed tomography; *p<0.001 *versus* partial and *versus* complete success in the CT group.

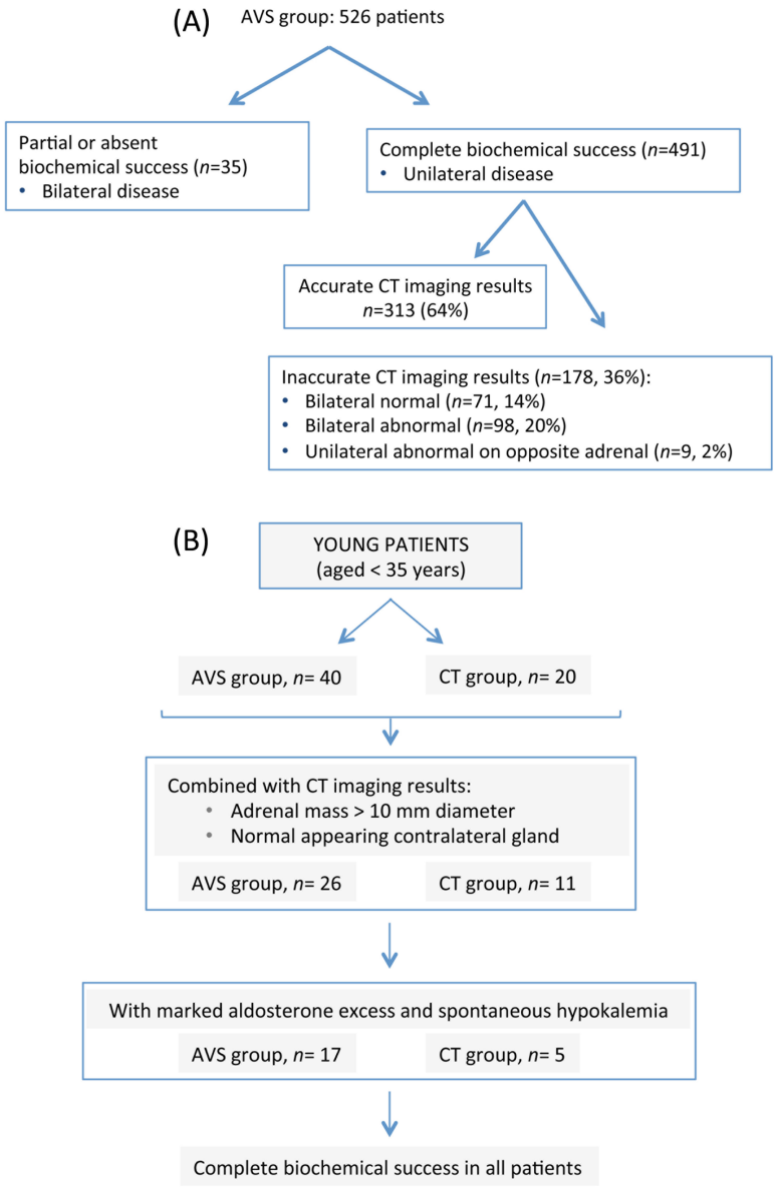

Figure 3. Reliability of CT compared with AVS for the diagnosis of unilateral primary aldosteronism.

A comparison of CT with AVS results in patients with AVS management who were biochemically cured after adrenalectomy (491 of 526 patients) indicated discordant findings in 36% of patients (*Panel A*); there were 40 and 20 patients aged less than 35 years of age in the AVS and CT groups, respectively. The CT results indicated that 26 and 11 patients in the AVS and CT groups had a unilateral adrenal mass (> 10 mm diameter), respectively, with a normal appearing contralateral adrenal. A marked phenotype of PA at baseline (plasma aldosterone concentration > 30 ng/dL and spontaneous hypokalemia) was observed in 17 (12 complete and 5 partial clinical success) and 5 (2 complete, 2

partial clinical success and 1 with missing clinical data) of these patients, all of whom were biochemically cured by adrenalectomy (*Panel B*).

AVS, adrenal venous sampling; CT, computed tomography.

Online-only supplement

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

Tracy A. Williams, Jacopo Burrello, Leonardo A. Sechi, et al.,

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

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

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

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

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

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

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

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

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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
Largest nodule at imaging	233	16 [11.0-22.0]	18 [12.0-26.3]	15 [10.0-20.0]	16 [9.8-20.0]	0.022

VARIABLE	N	ALL	CLINICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
(diameter, mm)						
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

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
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
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

VARIABLE	N	ALL	BIOCHEMICAL SUCCESS			*P*-value
			Complete	Partial	Absent	
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
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.

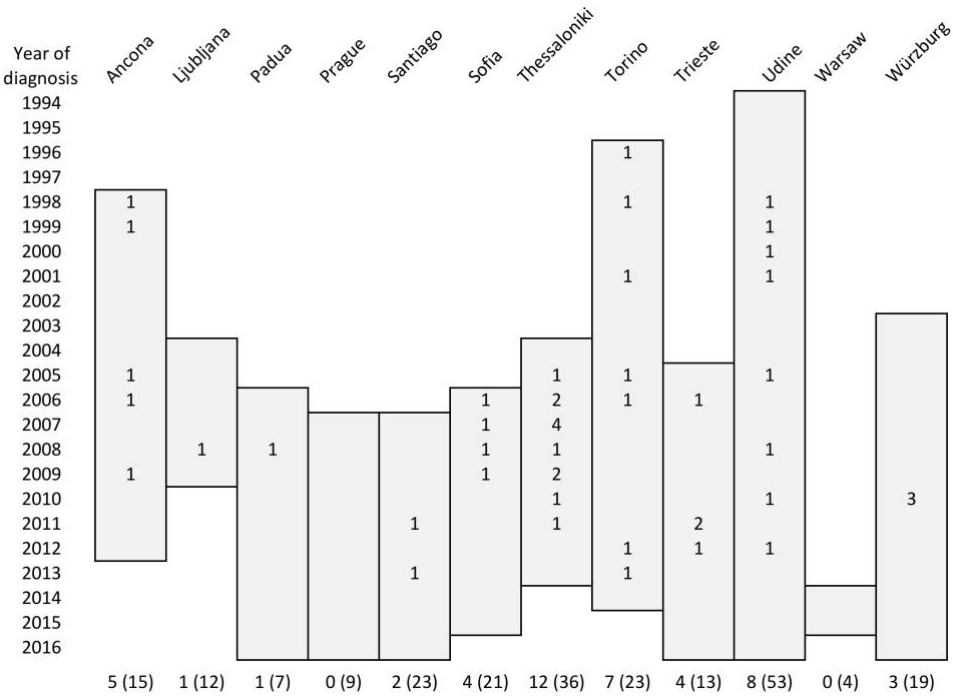

Figure S1. Timeline of absent and partial biochemical outcomes of patients with CT-based surgical decision.

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.

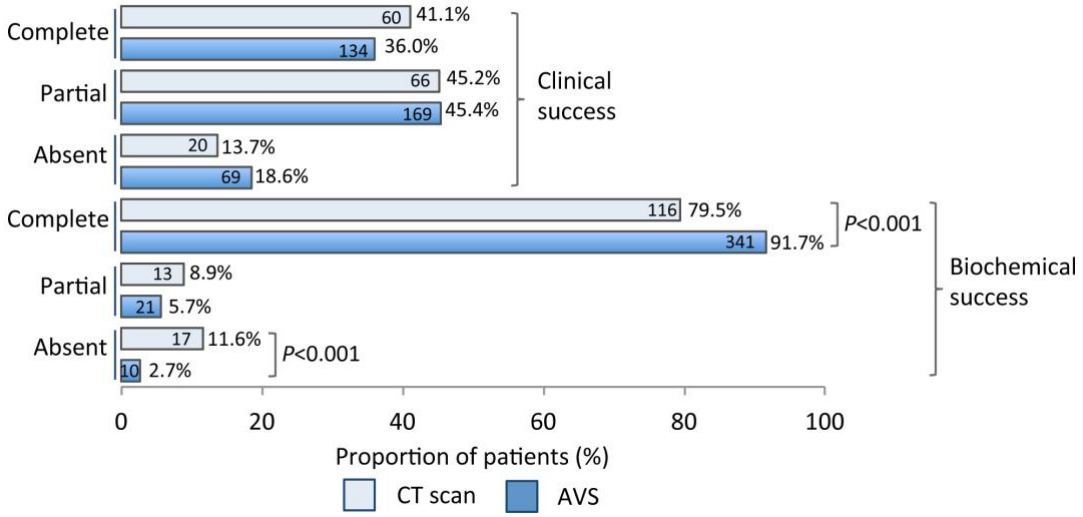

Figure S2. Subanalysis of clinical and biochemical outcomes of patients stratified by surgical management decision

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).

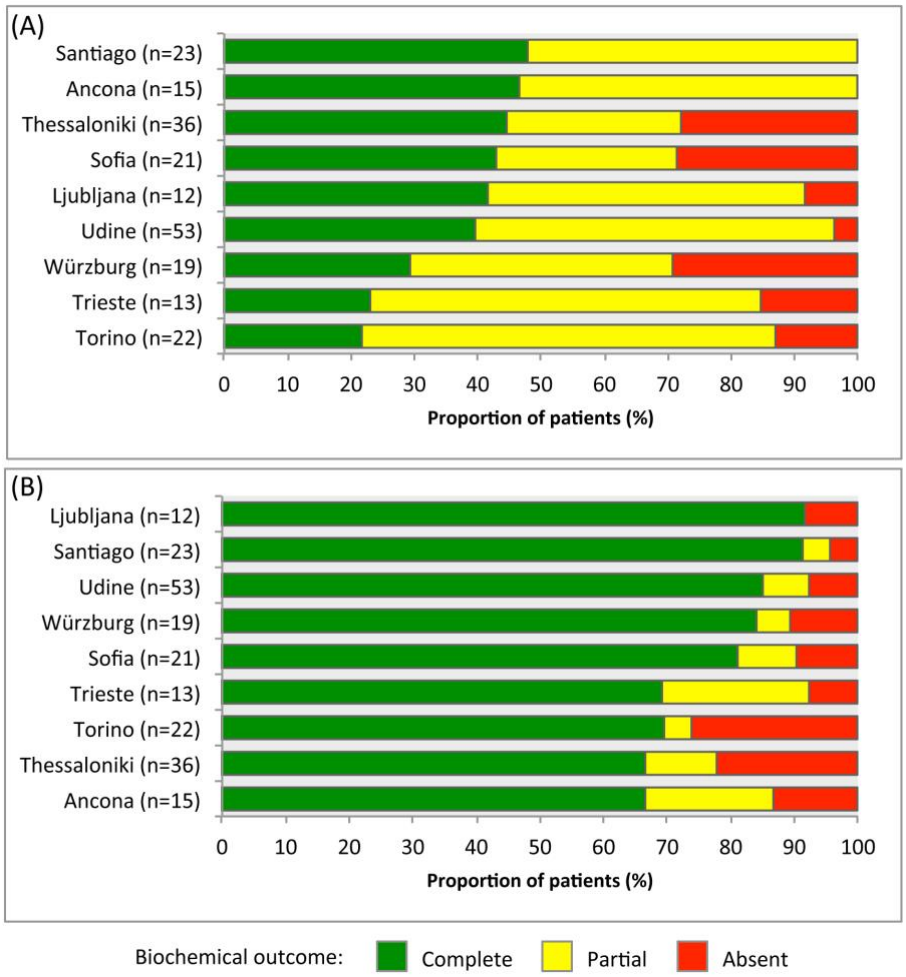

Figure S3. Clinical and biochemical outcomes of patients treated by adrenalectomy for unilateral primary aldosteronism with CT-based management.

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