Computed Tomography and Adrenal Venous Sampling in the Diagnosis of Unilateral Primary Aldosteronism

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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 (AVS) or computed tomography (CT). Our objective was to compare clinical and biochemical postsurgical outcomes of patients with unilateral primary aldosteronism diagnosed by CT or AVS and identify predictors of surgical outcomes. Patient data were obtained from 18 internationally distributed centers and retrospectively analyzed for clinical and biochemical outcomes of adrenalectomy of patients with surgical management based on CT (n=235 patients, diagnosed from 1994–2016) or AVS (526 patients, diagnosed from 1994–2015) using the standardized PASO (Primary Aldosteronism Surgical Outcome) criteria. Biochemical outcomes were highly different according to surgical management approach with a smaller proportion in the CT 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 CT was associated with a decreased likelihood of complete biochemical success compared with AVS (odds ratio, 0.28; 0.16–0.50; $P<0.001$). Clinical outcomes were not significantly different, but the absence of a postsurgical elevated aldosterone-to-renin ratio was a strong marker of complete clinical success (odds ratio, 14.81; 1.76–124.53; $P=0.013$) in the CT but not in the AVS group. In conclusion, patients diagnosed by CT have a decreased likelihood of achieving complete biochemical success compared with a diagnosis by AVS.

Key Words: adrenalectomy ■ aldosterone ■ hyperaldosteronism ■ prevalence ■ quality of life ■ renin

Primary aldosteronism (PA) is a frequent cause of secondary hypertension with a reported prevalence of 5% to 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 2 forms are preferentially treated by unilateral adrenalectomy or a mineralocorticoid receptor antagonist, respectively.[6,7] Unilateral PA is the most common surgically

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correctable cause of hypertension with a highly variable proportion of patients achieving clinical remission after surgery between centers.[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 early diagnosis and targeted treatment can minimize 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 differentiation of unilateral from bilateral PA is therefore mandatory for optimal clinical management and is widely undertaken by adrenal venous sampling (AVS) 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 about 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 nonfunctional adrenal incidentalomas.[6,22–27] For these reasons, AVS is recommended for the diagnostic workup of PA by the clinical practice guideline of the Endocrine Society.[6] The only randomized 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 2 approaches. A nonsignificant 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 workup 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 PASO (Primary Aldosteronism Surgical Outcome) consensus[10] and to identify predictors of outcomes.

Methods

The authors declare that all supporting data are available within the article and in the online-only Data Supplement.

An expanded Methods section is available in the online-only Data Supplement.

Patient Cohorts and Outcome Assessment

All 12 centers 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, and Yokohama). Data from 761 patients with unilateral PA were obtained (235 with CT management diagnosed from 1994–2016, and 526 with AVS management diagnosed from 1994–2015; Table S1 and Figure S1 in the online-only Data Supplement). 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) because of newly available outcome data. The CT group included all patients in each center 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 standardized criteria of the PASO consensus with follow-up at 6 to 12 months which are based on blood pressure measurements and antihypertensive drug dosage (clinical outcomes) and assessment of the aldosterone-to-renin ratio (ARR) and normalization of hypokalemia (if present presurgically; 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 SD, or as medians with interquartile ranges 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.

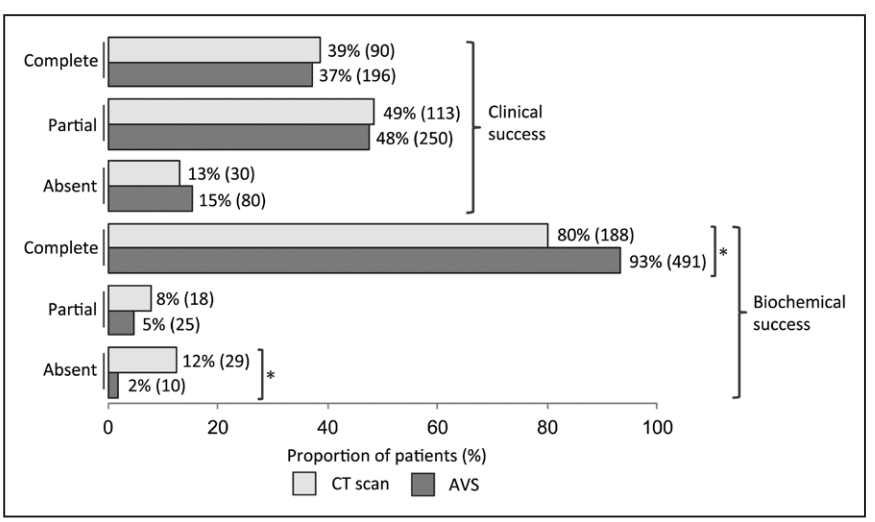

Figure 1. Clinical and biochemical outcomes of patients stratified by surgical management decision. Outcomes were assessed in accordance with the PASO (Primary Aldosteronism Surgical Outcome) consensus and are shown as proportions of patients (%) with absolute numbers in parenthesis for each clinical or biochemical outcome category (complete, partial, or absent). A total of 233 and 235 patients had clinical and biochemical outcome data, respectively in the computed tomography (CT) group and 526 patients had both clinical and biochemical outcome data in the adrenal venous sampling (AVS) group. *P<0.001.

Table 1. Clinical Variables of Patients Stratified by CT- or AVS-Based Management

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, y	761	50.4±11.1	49.3±11.3	50.9±11.0	0.068
Sex (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 per minute	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, mm Hg	760	154±21.4	159±18.8	152±22.2	<0.001
Diastolic BP, mm Hg	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 mellitus (yes), %	760	107 (14.1)	29 (12.4)	78 (14.8)	0.373
eGFR, mL/min per m^2	714	87±23.1	94±24.5	84±22.0	<0.001
Twenty-four hours albuminuria, mg/d	545	15.0 (9.9–50.0)	15.0 (10.0–62.8)	15.0 (9.0–49.3)	0.693
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 per minute	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, mm Hg	761	130±14.2	133±13.8	129±14.3	<0.001
Diastolic BP, mm Hg	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
Postoperative change (baseline–follow-up)					
ΔSystolic BP, mm Hg	760	24±21.2	26±18.3	23±22.4	0.140
ΔDiastolic BP, mm Hg	759	13±13.7	16±12.3	11±14.2	<0.001
ΔDDD	758	1.5 (0.5–3.0)	1.5 (0.7–2.5)	1.5 (0.5–3.0)	0.508

The Δ postoperative changes are calculated as baseline–follow-up as indicated. A positive value indicates a decrease and a negative value indicates an increase. ARR indicates aldosterone-to-renin ratio; ARR_DRC, ARR calculated using direct renin concentration; ARR_PRA, ARR calculated using PRA; AVS, adrenal venous sampling; BMI, body mass index; BP, blood pressure; CT, computed tomography; 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/]); DRC, direct renin concentration; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; and PRA, plasma renin activity.

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; Table 1). Similar clinical and biochemical outcomes were observed when the analysis was restricted to centers 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 postsurgical ARR (measured with plasma renin activity because direct renin concentration measurements may perform less well compared with plasma renin activity for low renin values)[30,31] was highly elevated in patients with an absent clinical outcome (107.1, interquartile range, 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 ARR stratified for clinical outcomes (Figure 2; Table S4).

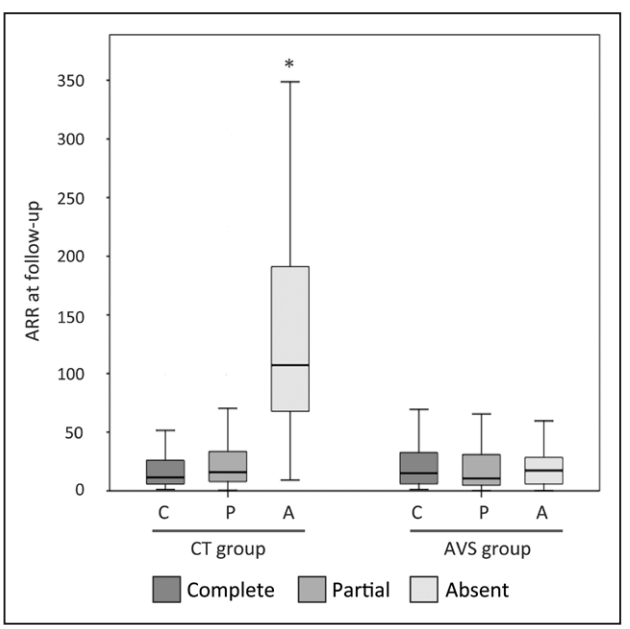

Figure 2. Stratification of the postsurgical aldosterone-to-renin ratio (ARR) by clinical outcomes and surgical management decision. The box and whisker plot shows the median aldosterone-to-renin ratio at follow-up (thick horizontal line within bars) derived from plasma renin activities stratified for clinical outcomes (C, complete; P, partial; and A, absent clinical success) in the computed tomography (CT) and adrenal venous sampling (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 assessed using the plasma renin activity. *$P<0.001$ vs partial vs complete success in the CT group.

Assessment of postsurgical outcomes across centers indicated less variance in clinical remission (22% to 48%) and a wider variance in biochemical remission (67% to 92%) with CT management 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 center (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, 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 body mass index) 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 odds ratio [OR], 0.28; 0.16–0.50; $P<0.001$). The approach to surgical management did not influence the likelihood of clinical outcomes (Table 2).

In the total cohort, the absence of an elevated ARR 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 postsurgical ARR 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 ARR 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 PA Including Young Patients <35 Years of Age

In the diagnostic workup of PA, CT scanning precedes AVS to exclude the presence of 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

Table 2. Clinical Variables Associated With Outcomes Stratified by CT- or AVS-Based Management Decision

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 y	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 1.73 m^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	NA	NA
CT group: complete+partial vs absent (reference: complete+partial)				
Age, per y	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 1.73 m^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	NA	NA
AVS group: complete vs partial+absent (reference: complete)				
Age, per y	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 1.73 m^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	NA	NA
Basis for surgery decision (ref: CT scan)	NA	NA	NA	NA
AVS group: complete+partial vs absent (reference: complete+partial)				
Age, per y	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 1.73 m^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	NA	NA
Basis for Surgery Decision (ref: CT scan)	NA	NA	NA	NA
AVS+CT group: complete vs partial+absent (reference: complete)				
Age, per y	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 1.73 m^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	NA	NA
Basis for surgery decision (ref: CT scan)	1.04 (0.67–1.60)	0.859	0.28 (0.16–0.50)	<0.001

(*Continued*)

Table 2. Continued

Variables	Clinical Outcome		Biochemical Outcome	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
AVS+CT group: complete+partial vs absent (reference: complete+partial)				
Age, per y	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 1.73 m^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	NA	NA
Basis for surgery decision (ref: CT scan)	1.85 (0.99–3.45)	0.053	0.15 (0.06–0.36)	<0.001

Logistic regressions identified factors associated with complete clinical and biochemical success. An odds ratio >1 shows an increased odds (or likelihood) of clinical or biochemical outcome, whereas an odds ratio of <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 >1 indicates a decreased odds and an odds ratio <1 means that the odds are increased. ARR indicates aldosterone-to-renin ratio; ARR at FU, aldosterone-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); AVS, adrenal venous sampling; BMI, body mass index; CI, confidence interval; CT, computed tomography; eGFR, estimated glomerular filtration rate; FU, follow-up; LVH, left ventricular hypertrophy; NA, not applicable: an elevated ARR is a criterion of partial and absent biochemical success; OR, odds ratio; and ref, reference.

(7.6% of 526) and 20 (8.5% of 235) patients aged <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 <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 >9 out of 10 patients and clinical remission or a marked improvement in clinical parameters in >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 preoperatively. 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 ARR which is a criterion of absent and partial biochemical success) in patients with a CT-based diagnosis was associated with unfavorable 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) is associated with unfavorable 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 preexisting 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 randomized design, was the assessment of outcomes in accordance with a standardized 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

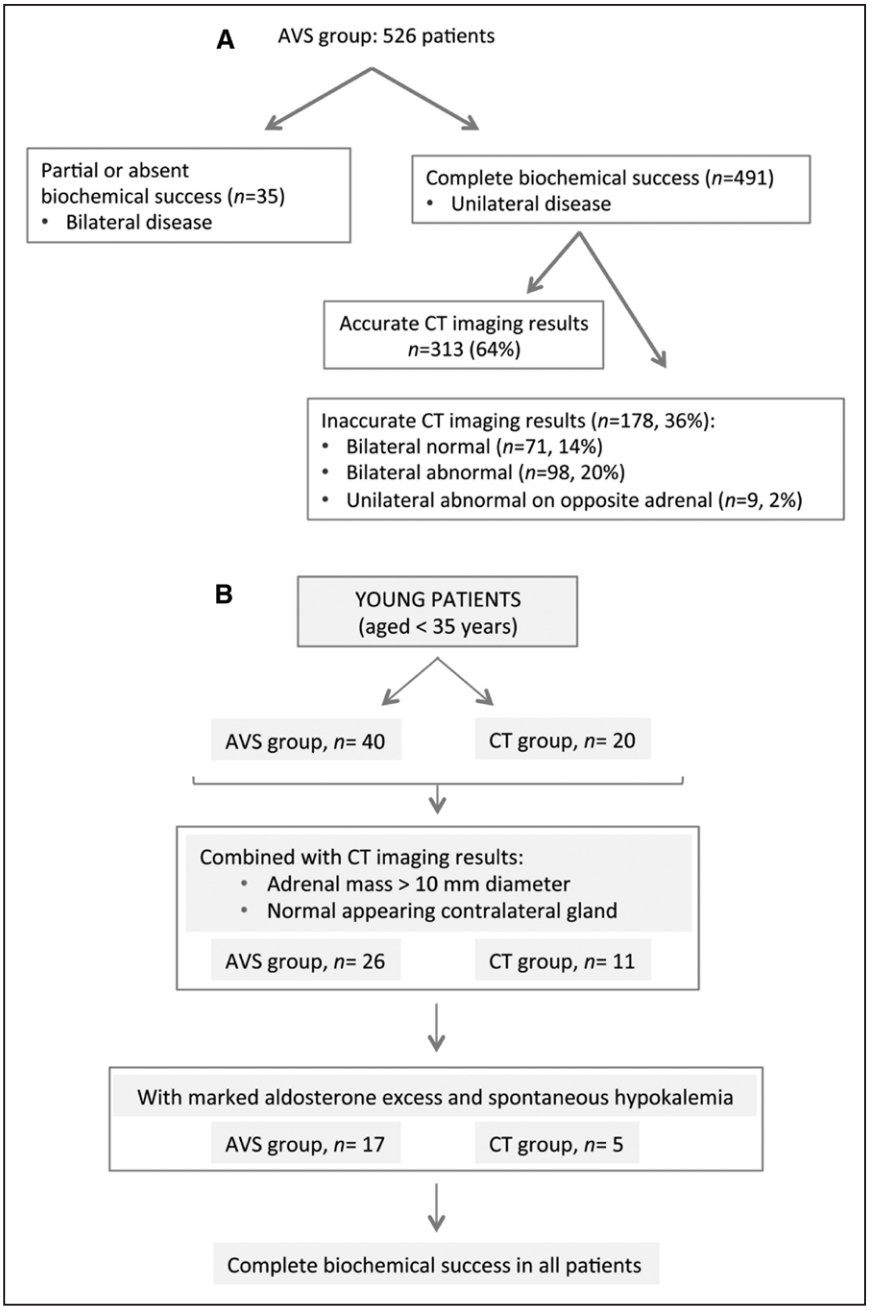

Figure 3. Reliability of computed tomography (CT) compared with adrenal venous sampling (AVS) for the diagnosis of unilateral primary aldosteronism. A comparison of CT with AVS results in patients with AVS management who were biochemically cured after adrenalectomy (491 of 526 patients) indicated discordant findings in 36% of patients (**A**); there were 40 and 20 patients aged <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 primary aldosteronism (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 (**B**).

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]

We demonstrate the lower performance of nonfunctional imaging compared with AVS for the diagnosis of lateralized aldosterone excess in unilateral PA. The high level of discordance between imaging and AVS results for determining lateralization in PA has been reported previously.[25,32] The present study is, however, the largest cohort to date that uses uniform (albeit post hoc) follow-up data assessed in accordance with an international consensus.[10] 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 <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

<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 was 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 centers with outcomes assessed in accordance with an internationally recognized 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 after 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 nonstandardized technique that is not available at all centers. However, the correct diagnosis and treatment of patients with unilateral forms offer a potential cure and the possibility to avoid comorbidities associated with long-term inappropriate aldosterone production.

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Disclosures

None.

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