Clinical outcomes after surgery for primary aldosteronism

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Clinical outcomes after surgery for primary aldosteronism: Evaluation of the PASO-investigators' consensus criteria within a worldwide cohort of patients

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ABSTRACT

Background: In a first step toward standardization, the Primary Aldosteronism Surgical Outcomes investigators introduced consensus criteria defining the clinical outcomes after adrenalectomy for primary aldosteronism. Within this retrospective cohort study, we evaluated the use of these consensus criteria in daily clinical practice in 16 centers in Europe, Canada, Australia, and the United States.

Methods: Patients who underwent unilateral adrenalectomy for primary aldosteronism between 2010 and 2016 were included. Patients with missing data regarding preoperative or postoperative blood pressure or their defined daily dose were excluded. According to the Primary Aldosteronism Surgical Outcomes criteria, patients were classified as complete, partial, or absent clinical success.

Results: A total of 380 patients were eligible for analysis. Complete, partial, and absent clinical success was achieved in 30%, 48%, and 22%, respectively. Evaluation of the Primary Aldosteronism Surgical Outcomes criteria showed that in 11% and 47% of patients with partial and absent clinical success, this classification was incorrect or debatable (16% of the total cohort). This concept of a "debatable classification of success" was due mainly to the cutoff of ≥20 mmHg used to indicate a clinically relevant change in systolic blood pressure and the use of percentages instead of absolute values to indicate a change in defined daily dose.

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Conclusion: Although introduction of the Primary Aldosteronism Surgical Outcomes consensus criteria induced substantial advancement in the standardization of postoperative outcomes, our study suggests that there is room for improvement in the concept for success given the observed limitations when the criteria were tested within our international cohort. In line, determining clinical success remains challenging, especially in patients with opposing change in blood pressure and defined daily dose.

Introduction

Primary aldosteronism (PA) is the most common surgically correctable cause of endocrine hypertension.[1,2] The prevalence of PA varies widely across studies, with an estimated prevalence around 5% within the general hypertensive population and could even exceed 20% in patients with resistant hypertension.[3–6] In the vast majority of cases, PA is either caused by bilateral adrenal hyperplasia or by a unilateral, aldosterone-producing adenoma (APA). Although bilateral hyperplasia is normally treated with a mineralocorticoid receptor agonist, adrenalectomy is the preferred treatment for patients with APA.[7] Because both hypertension and aldosteronism contribute independently to an increased risk on morbidity and mortality through end-organ damage, the ultimate goal of treatment is normalization of both parameters.[5,8–13]

From a patient's perspective, the immediate benefits of operative therapy include improvement in the control of blood pressure and a decrease in the burden of the need for antihypertensive drugs. Complete clinical success (ie, normalization of blood pressure without the need for antihypertensive medications) is achieved in ≤50%.[14–18] Patients without complete clinical success, however, may also benefit from surgery through a decrease in systolic blood pressure (SBP) or in their medications, with a subsequent decrease in morbidity and drug burden.[19,20] This decrease in SBP is potentially very important because every decrease of 10 mmHg in SBP leads to a risk reduction of 20% in cardiovascular morbidity and a risk reduction of 13% in all-cause mortality in patients with hypertension. This risk reduction is shown across various levels of baseline blood pressure and is, therefore, not associated with crossing the blood pressure threshold that currently defines hypertension.[20]

In the past, studies on clinical outcomes after surgery for PA were limited by a lack of standardized outcome definitions, making it difficult to interpret or compare results.[14–18] As a response, the Primary Aldosteronism Surgical Outcomes (PASO) investigators established clear and feasible definitions for these outcomes by using a Delphi method.[15] Clinical response after adrenalectomy was defined as either being complete, partial, or absent based on a decrease in both blood pressure and antihypertensive medications. In this stratification, patients with partial clinical response are not completely cured, but still benefit from surgery through a decrease in SBP ≥20 mmHg or decrease of ≥50% in their defined daily dose (DDD). Complete and partial clinical success were observed in 37% and 47% of patients, indicating that the majority of patients benefit from surgery regardless of potential concomitant biochemical cure.[15]

Although the PASO consensus criteria are a valuable step toward a global standardization of outcomes after surgery for PA, we hypothesized that these criteria might incorrectly classify patients as either partial or absent clinical success because of the use of percentages instead of absolute values to implicate a change in DDD. Furthermore, because a 10 mmHg decrease in SBP induces a substantial decrease in cardiovascular morbidity and mortality, one might also argue that the cutoff of ≥20 mmHg used to indicate a clinically relevant change in SBP is too conservative.[20] Likewise, this relatively high cutoff could also imply that patients with a relatively high increase in SBP (eg, 18 or 19 mmHg) would still be classified as a partial success when combined with a DDD decrease ≥50%. Therefore, we set out to evaluate the PASO consensus criteria for clinical outcomes in a large cohort reflecting current daily practice in Europe, Canada, Australia, and the United States.

Methods

Patients

We performed a retrospective cohort study across 16 medical referral centers in Europe, Canada, Australia, and the United States (Fig 1). The description and outcomes of this study cohort have been reported before.[21] In general, consecutive patients who underwent unilateral total adrenalectomy for APA between 2010 and 2016 were included. Biochemical evidence for PA was based on the aldosterone-to-renin ratio (ARR); however, no strict inclusion or exclusion criteria were used regarding biochemical confirmation of the disease. ARR indicating PA was defined as an ARR greater than the local reference range. Unilateral disease was diagnosed on computed tomography (CT) or magnetic resonance imaging (MRI) or adrenal venous sampling (AVS), according to each center's preference and availability. Patients with missing preoperative or follow-up data regarding SBP, diastolic blood pressure (DBP), or DDD were excluded. The grading of hypertension was based on blood pressure with medication.[22,23] To compare laboratory data between centers, absolute values were translated to either being normal, increased, or suppressed based on the local reference ranges. Hypokalemia was defined as either a potassium level less than the local reference range or the use of potassium supplementation. Data collection was performed separately within each center, with the use of a standardized data entry manual. All data were reviewed by the supervising investigators and revised by the participating centers. Institutional review board approval was obtained in all participating centers.

Outcomes

The aim of this study was to evaluate the PASO consensus criteria for clinical outcomes after adrenalectomy for PA within a study cohort reflecting current daily practice. Detailed presentation of the blood pressure–related outcomes within this study cohort were published earlier.[21] Some of these outcomes were analyzed and presented again within this study to enable thorough evaluation of the PASO consensus criteria. In addition to evaluation of the PASO consensus criteria, we also investigated the influence of decreasing the cutoff indicating what we consider to be a more clinically relevant change in SBP to ≥10 mmHg.

Definitions

Office blood pressure measurements were performed during outpatient visitation. If multiple preoperative or postoperative blood pressure measurements were performed (on the same antihypertensive medications), then the mean SBP and DBP were calculated. Antihypertensive medications were expressed as DDD, which is the assumed average maintenance dose per day for a drug used for its

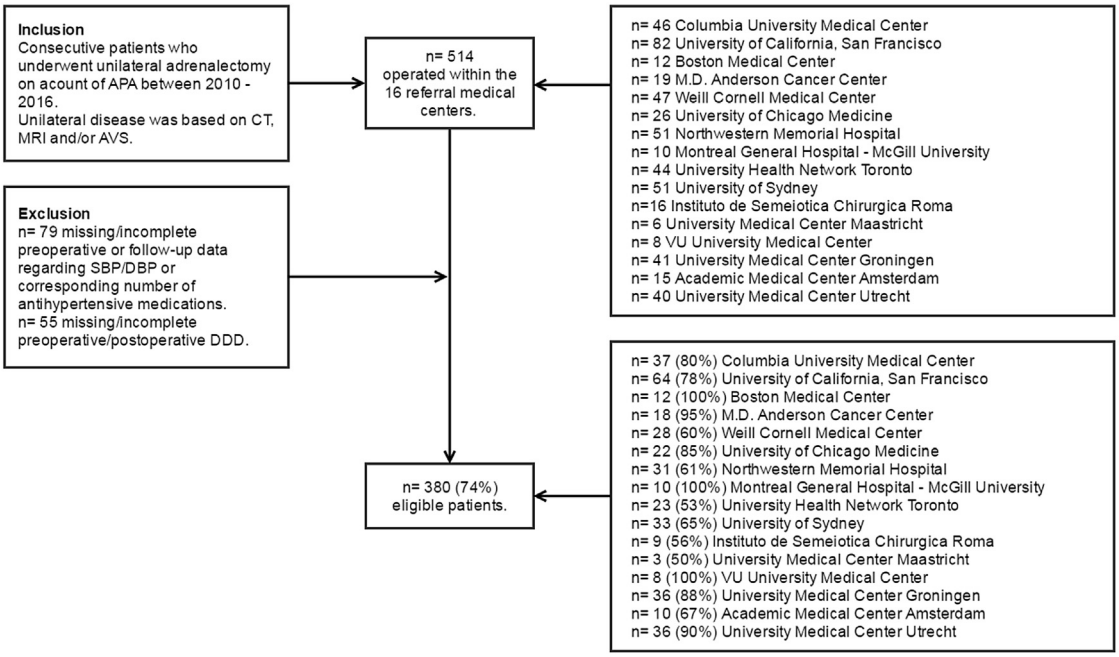

Fig 1. Flowchart of included patients from 16 referral centers.

main indication in adults. Calculation of DDD was based on the World Health Organization Anatomical Therapeutic Chemical/DDD index 2017 (see https://www.whocc.no/atc_ddd_index/). When antihypertensive medications were discontinued because of diagnostics testing, such as the ARR or a confirmatory test, blood pressure and corresponding medications before discontinuation were used. In line with the PASO consensus criteria, complete clinical success was defined as a postoperative normal blood pressure without the aid of antihypertensive medications. Partial clinical success was defined as either the same blood pressure as before surgery on a lesser DDD or a decrease in blood pressure on the same DDD. In case of increased blood pressure, increased DDD, unchanged blood pressure without a decrease in DDD, or unchanged DDD without a decrease in blood pressure, patients were classified as absent clinical success. Unchanged blood pressure was defined as a difference in (preoperative versus postoperative) SBP of <20 mmHg or DBP of <10 mmHg. A decrease or increase in blood pressure was defined as a difference in SBP of ≥20 mmHg or DBP of ≥10 mmHg. If a change in SBP and an opposing change in DBP were reported, the blood pressure response was defined by the change in SBP. Unchanged antihypertensive medications (preoperative versus postoperative) was defined as a change of <50% in DDD and increased or decreased antihypertensive medications as a change of ≥50%.[15] Evaluation of this PASO classification was performed by critical examination of the absolute change in blood pressure and DDD within each patient. When a classification was indicated as "debatable," this finding was due mainly to an opposing change in blood pressure and antihypertensive medications without the one clearly surpassing the other. Our goal was to assess outcomes at follow-up closest to 6 months (range 3–6 months) after adrenalectomy. Mainly owing to geographic distances and referral patterns, multiple medical centers were not able to complete this 6 months of follow-up. To prevent for a high percentages of lost to follow-up, we also included patients who underwent follow-up during other follow-up periods.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). The χ^2 test and the Fisher exact test were used to analyze group differences for categorical variables. For comparisons between more than two groups, one-way ANOVA was used for normally distributed data, and the Kruskal-Wallis test was used for not normally distributed data. To observe differences between groups and to account for multiple testing after one-way ANOVA, a multiple-comparison, post hoc Bonferroni correction was used. A P value of <.05 was considered statistically significant. Statistical analysis was performed using SPSS v 23.0 (IBM Corp, Armonk, NY, USA) and figures were constructed using Graphpad Prism v 7.02 (GraphPad Software Inc, LaJolla, CA, USA).

Results

A total of 514 patients were identified in 16 participating referral centers, and 380 (74%) were eligible for inclusion (Fig 1). The median number of included patients per center was 23 (IQR 10–35). Baseline characteristics of the cohort are presented in Table I. The preoperative and postoperative blood pressures were an average of 2 or more separate measurements in 73% and 50% of patients, respectively. The ARR was increased in 95% of patients and CT, AVS, and MRI were performed in 88%, 64%, and 17% of patients, respectively.

Clinical success

Complete, partial, and absent clinical success were observed in 112 (30%), 183 (48%), and 85 (22%) patients, respectively (Table II). Per medical center, complete, partial, and absent clinical success were observed in a median of 30% (IQR 19%–43%), 48% (IQR 35%–57%), and 24% (IQR 12%–36%), respectively (Supplementary Fig).

In the total cohort, the mean SBP and DBP decreased by 16 (±21) mmHg and 7 (±14) mmHg after surgery (Table II). Furthermore, a DDD decrease of 2.0 (IQR 0.7–4.0) and decrease in number of pills per day by 2 (IQR 1–3) were observed. Although patients with complete success had a significantly lower baseline SBP, DBP, and DDD compared with patients with partial success, the postoperative decreases in SBP, DBP, and DDD were comparable

Table 1
Baseline characteristics of 380 patients

Variable	Total cohort ($n = 380$)	Clinical success			Overall P value	Pairwise comparison P values		
	Number (%) or mean ± SD	Complete ($n = 112$)(30%)	Partial ($n = 183$)(48%)	Absent ($n = 85$)(22%)		Complete versus partial	Complete versus absent	Partial versus absent
		Number (%) or mean ± SD	Number (%) or mean ± SD	Number (%) or mean ± SD				
Age at surgery (years)	50 ± 11	46 ± 10	52 ± 11	51 ± 11	**<.001**	**<.001**	**.004**	.859
Sex								
Female	165 (43)	73 (65)	62 (34)	30 (35)	**< .001**	**< .001**	**< .001**	.820
Male	215 (57)	39 (35)	121 (66)	55 (65)				
Duration of HTN (years; $n = 321$)*	8 [3–12]	5 [2.3–10]	9 [4.5–14]	10 [5–12.8]	**< .001**	**< .001**	**< .003**	1.000
Body mass index ($n = 350$)	30 ± 6	27 ± 5	30 ± 6	31 ± 5	**< .001**	**< .001**	**< .001**	1.000
DDD preoperative*	3.7 [2.0–5.6]	2.2 [1.2–3.5]	4.3 [2.7–6.5]	4.0 [2.2–6.0]	**< .001**	**< .001**	**< .001**	.267
Hypokalemia ($n = 374$)	275/374 (74)	77/110 (70)	140/179 (78)	58/85 (68)	.139	.117	.791	.080
History of CV events ($n = 377$)	54/377 (14)	6/111 (5)	33/182 (18)	15/84 (18)	**.006**	**.002**	**.005**	.957
Diabetes ($n = 378$)	50/378 (13)	6/111 (5)	32/182 (18)	12/85 (14)	**.011**	**.003**	**.036**	.477
Current smoker ($n = 367$)	38/367 (10)	8/109 (7)	25/177 (14)	5/81 (6)	.071	.081	.753	.064
Hypercholesterolemia ($n = 377$)	96/377 (26)	11/111 (10)	60/182 (33)	25/84 (22)	**< .001**	**< .001**	**< .001**	.602
FA history of HTN ($n = 298$)	150/298 (50)	34/82 (42)	75/145 (52)	41/71 (58)	.119	.137	**.045**	.404
Preoperative mean systolic blood pressure with medication (mmHg)	150 ± 19	142 ± 16	157 ± 20	143 ± 15	**< .001**	**< .001**	1.000	**< .001**
Preoperative mean diastolic blood pressure with medication (mmHg)	90 ± 13	88 ± 11	92 ± 14	87 ± 10	**.001**	**.014**	1.000	**.005**
JNC/ESH hypertension grade based on blood pressure with medication					**< .001**	**< .001**	.106	**< .001**
Grade 0	101 (27)	47 (42)	28 (15)	26 (31)				
Grade 1	156 (41)	39 (35)	76 (42)	41 (48)				
Grade 2	91 (24)	23 (21)	50 (27)	18 (21)				
Grade 3	32 (8)	3 (3)	29 (16)	0				
Increased aldosterone level ($n = 353$)	193/353 (55)	66/104 (64)	92/172 (54)	35/77 (46)	.050	.105	**.016**	.241
Suppressed renin level/activity ($n = 318$)	214/318 (67)	67/91 (74)	102/157 (65)	45/70 (64)	.312	.158	.202	.912
ARR indicating PA ($n = 309$)	292/309 (95)	83/86 (97)	145/154 (94)	64/69 (93)	.574	.422	.468	.690
Increased creatinine level ($n = 345$)	60/345 (17)	9/104 (9)	39/165 (24)	12/76 (16)	**.006**	**.002**	.141	.166
CT performed ($n = 377$)	330/377 (88)	101/111 (91)	157/182 (86)	72/84 (86)	.419	.226	.249	.904
AVS performed ($n = 379$)	241/379 (64)	70/111 (63)	115/183 (63)	56/85 (66)	.882	.970	.683	.630
MRI performed ($n = 379$)	64/379 (17)	21/112 (19)	33/182 (18)	12/85 (12)	.356	.894	.182	.187
Operative procedure					.123	.945	.074	.064
EPRA	152 (40)	48 (43)	75 (41)	29 (34)				
ELRA	52 (14)	12 (11)	21 (12)	19 (22)				
LTA	176 (46)	52 (46)	87 (48)	37 (44)				
Robot assisted	14 (4)	8 (7)	5 (3)	1 (1)	.056	.073	.081	.668
Histology ($n = 378$)					**.004**	**.007**	**.003**	.199
Adenoma	313/378 (83)	104/112 (93)	145/183 (79)	64/83 (77)				
Hyperplasia	53/378 (14)	6/112 (5)	29/183 (16)	18/83 (22)				
Adenoma/hyperplasia	12/378 (3)	2/112 (2)	9/183 (5)	1/83 (1)				
Hospital stay (days; $n = 378$)*	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	.347	.329	.163	.479

Significant P values are indicated in bold.
HTN, hypertension; *CV*, cardiovascular; *FA*, family; *JNC*, Joint National Commission; *ESH*, European Society of Hypertension; *PA*, primary aldosteronism; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *EPRA*, endoscopic posterior retroperitoneal adrenalectomy; *ELRA*, endoscopic lateral retroperitoneal adrenalectomy; *LTA*, laparoscopic transabdominal adrenalectomy.
* Values not normally distributed given as medians (IQR).

between both groups: 20 vs 22 mmHg ($P > .999$), 10 vs 8 mmHg ($P = .0.999$) and 2.2 vs 2.5 ($P = .124$), respectively (Table II). Postoperative serum potassium and aldosterone levels were measured in 96% and 65% of patients. Postoperative hypokalemia and hyperaldosteronism after adrenalectomy were observed in 13% and 5% of patients, respectively. The rates of clinical success were comparable between patients with and without a postoperative aldosterone measurement ($P = .992$) and patients with and without postoperative hyperaldosteronism ($P = .717$).

Influence of AVS and duration of follow-up on outcomes

Comparing patients with and without a preoperative AVS showed complete, partial, and absent clinical success in 29%, 48%, and 23% vs 30%, 49%, and 21% of patients, respectively ($P = .865$). Hyperplasia on histology was shown in 16% vs 11% of patients with and without AVS ($P = .393$). Patients with AVS did not show better outcomes regarding postoperative hypokalemia ($P = .474$) and hyperaldosteronism ($P = .552$). Final outcomes were assessed between 3 and 9 months after adrenalectomy in most patients (64%), but there also were a substantial number of patients with <1 month of follow-up (23%). Nevertheless, no clear differences in rates of clinical success ($P = .817$; Fig 2), change in SBP ($P = .332$), nor change in DDD ($P = .132$) were shown between the periods of follow-up. After exclusion of the 23% of patients with follow-up <1 month, the rates of complete, partial, and absent clinical success remained unchanged in 30%, 48%, and 22%, respectively. Also, within this cohort, no differences in the rates of clinical success between patients with and without preoperative AVS were observed ($P = .959$). Only selecting patients with 3 to 9 months follow-up and preoperative AVS resulted in comparable rates of complete, partial, and absent clinical success of 30%, 47%, and 23%, respectively.

Table II
Effect of surgery on blood pressure and use of antihypertensive medications

Variable	Total cohort ($n = 380$)	Clinical success			Overall *P* value	Pairwise comparison *P* value		
	Number (%) or mean ± SD	Complete ($n = 112$)(30%)	Partial ($n = 183$)(48%)	Absent ($n = 85$)(22%)		Complete versus partial	Complete versus absent	Partial versus absent
		Number (%) or mean ± SD	Number (%) or mean ± SD	Number (%) or mean ± SD				
Systolic blood pressure								
Preoperative mean (mmHg)	150 ± 19	142 ± 16	157 ± 20	143 ± 15	**< .001**	**< .001**	1.000	**< .001**
Postoperative mean (mmHg)	133 ± 17	122 ± 9	136 ± 16	143 ± 18	**< .001**	**< .001**	**< .001**	**< .001**
Pre-post Delta mean (mmHg)	16 ± 21	20 ± 17	22 ± 20	1 ± 19	**< .001**	1.000	**< .001**	**< .001**
Pre-post Delta mean (%; ± SD)	10% ± 13%	13% ± 11%	13% ± 14%	0% ± 14%	**< .001**	1.000	**< .001**	**< .001**
Diastolic blood pressure								
Preoperative mean (mmHg)	90 ± 13	88 ± 11	92 ± 14	87 ± 10	**.001**	**.014**	1.000	**.005**
Postoperative mean (mmHg)	83 ± 10	78 ± 7	84 ± 11	86 ± 11	**< .001**	**< .001**	**< .001**	.428
Pre-post Delta mean (mmHg)	7 ± 14	10 ± 11	8 ± 15	1 ± 12	**< .001**	1.000	**< .001**	**< .001**
Pre-post Delta mean (%; ± SD)	7% ± 14%	10% ± 13%	8% ± 14%	1% ± 14%	**< .001**	.691	**< .001**	**< .001**
JNC/ESH hypertension grade								
Preoperative								
Grade 0	101 (27)	47 (42)	28 (15)	26 (31)	**< .001**	**< .001**	.106	**< .001**
Grade 1	156 (41)	39 (35)	76 (42)	41 (48)				
Grade 2	91 (24)	23 (21)	50 (27)	18 (21)				
Grade 3	32 (8)	3 (3)	29 (16)	0				
Postoperative								
Grade 0	236 (62)	112 (100)	89 (49)	35 (41)	**< .001**	**< .001**	**< .001**	**.028**
Grade 1	103 (27)	0 (0)	74 (40)	29 (34)				
Grade 2	33 (9)	0 (0)	17 (9)	16 (19)				
Grade 3	8 (2)	0 (0)	3 (2)	5 (6)				
Daily defined dose								
Preoperative DDD*	3.7 [2.0–5.7]	2.2 [1.2–3.5]	4.3 [2.7–6.5]	4.0 [2.1–6.0]	**< .001**	**< .001**	**< .001**	.267
Postoperative DDD*	1.0 [0–3.0]	0.0 [0.0–0.0]	1.5 [0.3–3.0]	3.0 [2.0–5.0]	**< .001**	**< .001**	**< .001**	**< .001**
Pre-post Delta DDD*	2.0 [0.7–4.0]	2.2 [1.2–3.5]	2.5 [1.0–5.0]	0.7 [0.0–2.0]	**< .001**	.625	**< .001**	**< .001**
Pre-post Delta DDD (%)*	74% [27–100]	100% [100–100]	67% [41–90]	20% [0–40]	**< .001**	**< .001**	**< .001**	**< .001**
Number of pills per day ($n = 378$)								
Preoperative (number/day)*	3 [2–5]	2 [1–3]	4 [2–5]	3 [2–5]	**< .001**	**< .001**	**< .001**	.339
Postoperative (number/day)*	1 [0–2]	0 [0–0]	1 [1–3]	2 [1–3.5]	**< .001**	**< .001**	**< .001**	**.014**
Pre-post Delta (number/day)*	2 [1–3]	2 [1–3]	2 [1–3]	1 [0–2]	**< .001**	1.000	**< .001**	**< .001**
Pre-post Delta (%)*	67% [33–100]	100% [100–100]	56% [33–80]	25% [0–50]	**< .001**	**< .001**	**< .001**	**< .001**

Significant *P* values are indicated in bold.
JNC, Joint National Commission; *ESH*, European Society of Hypertension.
* Values not normally distributed given as medians (IQR).

Evaluation of the PASO consensus criteria

Table III presents an overview of the magnitude of change in SBP after surgery within the total cohort and within complete, partial, or absent clinical success. In the subgroup classified as complete success, only 3 patients (3%) had an increase of SBP ≥10 mmHg; however, these patients were still normotensive postoperatively without antihypertensive medications. Moreover, within these patients, the DDD also decreased substantially by 2.8, 5.0, and 6.5, respectively. Furthermore, all patients with an SBP increase between 1 and 9 mmHg had a substantial decrease of DDD, indicating clear complete success. Further examination showed appropriate classification when using the PASO criteria within all patients with complete clinical success.

Among the patients with partial and absent success, however, examination of the change in SBP and DDD revealed that, in 11% and 47% of patients classified as partial and absent clinical success, this classification was incorrect or debatable (16% of the total cohort).

Supplementary Table I presents all patients classified as a partial clinical success with an incorrect or a debatable classification. Within this subgroup, 10 patients had an increase in SBP of between 10 and 19 mmHg, indicating that these patients would have been classified as absent clinical success when using a ≥10 mmHg instead of a ≥20 mmHg cutoff point, indicating clinically relevant change in SBP (Table III); however, among these patients, the DDD decreased by a median of 3.6 DDD (IQR 2.2–5.0), with a minimum of 1.8 making classification as either partial or absent success debatable because of the opposing change in SBP and DDD (Supplementary Table I). One of the 15 patients with an increase of SBP between 1 and 9 mmHg was certainly classified incorrectly as partial success. Although the DDD decrease in this patient was 50%, there was only a 0.3 decrease in the absolute DDD value. Therefore, this patient should be classified as absent success (Supplementary Table I). The other 14 patients showed a high decrease in DDD by a median 4.8 (IQR 2.7–6.9), with a minimum of 1.7. By our interpretation, this surpassed the increase in SBP, indicating a clear partial success. Furthermore, 9 patients with partial success

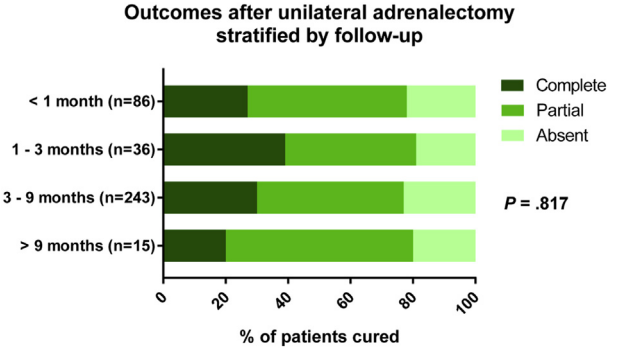

Fig 2. Outcomes after unilateral adrenalectomy stratified by moment of follow-up.

Table III
Distribution of magnitude of change in blood pressure within complete, partial, and absent clinical success

Postoperative change in systolic blood pressure	Total cohort ($n = 380$)	Clinical success					
		PASO criteria			When SBP $\geq$ 10 mmHg*		
		Complete ($n = 122$) (30%)	Partial ($n = 183$) (48%)	Absent ($n = 85$) (22%)	Complete ($n = 122$) (30%)	Partial ($n = 199$) (52%)	Absent ($n = 69$) (18%)
40–49 mmHg	3 (1%)	0 (0%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	3 (4%)
30–39 mmHg	4 (1%)	0 (0%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)	4 (6%)
20–29 mmHg	10 (3%)	1 (<1%)	0 (0%)	9 (11%)	1 (<1%)	0 (0%)	9 (13%)
10–19 mmHg	22 (6%)	2 (2%)	**10 (6%)**	**10 (12%)**	2 (2%)	**0 (0%)**	**20 (29%)**
1–9 mmHg	28 (7%)	8 (7%)	15 (8%)	5 (6%)	8 (7%)	15 (8%)	5 (7%)
Increase ↑							
Decrease ↓							
0–9 mmHg	66 (17%)	20 (18%)	27 (15%)	19 (22%)	20 (18%)	27 (14%)	19 (28%)
10–19 mmHg	80 (21%)	22 (20%)	**31 (17%)**	**27 (32%)**	22 (20%)	**57 (29%)**	**1 (1%)**
20–29 mmHg	76 (20%)	28 (25%)	41 (22%)	7 (8%)	28 (25%)	41 (21%)	7 (10%)
30–39 mmHg	47 (12%)	18 (16%)	29 (16%)	0 (0%)	18 (16%)	29 (15%)	0 (0%)
40–49 mmHg	22 (6%)	7 (6%)	14 (8%)	1 (1%)	7 (6%)	14 (7%)	1 (1%)
$\geq$50 mmHg	22 (6%)	6 (5%)	16 (9%)	0 (0%)	6 (5%)	16 (8%)	0 (0%)

* Distribution of magnitude of change in blood pressure within complete, partial and absent clinical success when change of blood pressure would be defined as an increase or decrease of $\geq$10 mmHg in SBP compared with $\geq$20 mmHg used in the PASO consensus criteria.

Table IV
Patients classified as absent clinical success according to the PASO criteria but with a clinically relevant decrease in blood pressure or antihypertensive medications

Preoperative		Postoperative			Change			Clinical success		
DDD	BP (mmHg)	DDD	BP (mmHg)	FU (months)	DDD	DDD (%)	SBP (mmHg)	PASO	SBP $\geq$ 10	Interpretation
26 patients with 10–19 mmHg SBP decrease however classified as absent success because of change in DDD <50% and SBP <20 mmHg										
11.0	144/82	10.8	133/81	< 1	−0.2	−2%	−11	Absent	Partial	Classification debatable
2.7	137/83	2.0	123/80	< 1	−0.7	−25%	−14	Absent	Partial	Incorrectly classified*
6.8	139/77	4.0	124/76	< 1	−2.8	−41%	−15	Absent	Partial	Incorrectly classified*
7.5	163/98	7.5	148/89	< 1	0.0	0%	−15	Absent	Partial	Incorrectly classified*
0.7	159/103	0.7	140/91	< 1	0.0	0%	−19	Absent	Partial	Incorrectly classified*
2.7	145/96	2.0	128/82	1–3	−0.7	−25%	−17	Absent	Partial	Incorrectly classified*
4.0	164/98	3.7	154/105	3–9	−0.3	−8%	−10	Absent	Partial	Classification debatable
2.5	145/80	2.5	135/87	3–9	0.0	0%	−10	Absent	Partial	Classification debatable
4.3	154/83	3.6	143/84	3–9	−0.7	−16%	−11	Absent	Partial	Incorrectly classified*
6.0	142/91	3.7	131/79	3–9	−2.3	−39%	−11	Absent	Partial	Incorrectly classified*
8.7	134/75	8.7	123/69	3–9	0.0	0%	−11	Absent	Partial	Classification debatable
0.0	161/103	0.0	150/98	3–9	0.0	0%	−11	Absent	Partial	Classification debatable
8.0	146/82	5.5	134/89	3–9	−2.5	−31%	−12	Absent	Partial	Incorrectly classified*
6.0	149/76	4.7	136/81	3–9	−1.3	−22%	−13	Absent	Partial	Incorrectly classified*
1.8	139/90	1.0	125/89	3–9	−0.8	−45%	−14	Absent	Partial	Incorrectly classified*
5.0	149/76	3.7	135/85	3–9	−1.3	−27%	−14	Absent	Partial	Incorrectly classified*
5.0	152/97	4.0	138/80	3–9	−1.0	−20%	−14	Absent	Partial	Incorrectly classified*
8.7	130/90	6.0	115/80	3–9	−2.7	−31%	−15	Absent	Partial	Incorrectly classified*
2.0	150/85	1.7	135/75	3–9	−0.3	−18%	−15	Absent	Partial	Incorrectly classified*
3.0	144/86	3.0	127/84	3–9	0.0	0%	−17	Absent	Partial	Incorrectly classified*
11.7	142/96	11.7	125/50	3–9	0.0	0%	−17	Absent	Partial	Incorrectly classified*
5.7	170/105	4.7	153/105	3–9	−1.0	−18%	−17	Absent	Partial	Incorrectly classified*
4.8	150/90	2.5	132/84	3–9	−2.3	−48%	−18	Absent	Partial	Incorrectly classified*
3.7	149/90	3.7	130/70	3–9	0.0	0%	−19	Absent	Partial	Incorrectly classified*
3.7	153/84	2.5	140/80	> 9	−1.2	−32%	−13	Absent	Partial	Incorrectly classified*
3.0	160/89	2.0	144/92	> 9	−1.0	−33%	−16	Absent	Partial	Incorrectly classified*

BP, Blood Pressure; *FU*, follow-up
* Patient should have been classified as partial success.

demonstrated a decrease in SBP; however, these patients also had a postoperative increase in DDD and a high absolute value of DDD. Therefore, classification of these patients could be debated (Supplementary Table I). All patients with a postoperative decrease in SBP between 0 and 9 mmHg also had a clinically relevant decrease in DDD, indicating clear partial success.

In 40 of the 85 (47%) patients classified as absent clinical success, the PASO classification was incorrect or open to debate (Supplementary Table II). Within this subgroup, 26 of the 27 patients with a postoperative decrease in SBP ranging from 10 to 19 mmHg also had a decreased (or equal) postoperative DDD; however, because this decrease in DDD was <50% and the decrease in SBP was <20 mmHg, these patients were classified as absent success according to the PASO criteria (Table IV). When using a $\geq$10-mmHg change in SBP as a cutoff point, these patients would be classified as partial clinical success (Tables III and IV). In our opinion, classification of those patients as absent success was most likely incorrect because a clear decrease in both blood pressure and medications was shown. The remaining patient showed a decrease in SBP of 19 mmHg together with an increase in DDD from 1.3 to 5.0 and therefore was classified correctly as absent success because of the high increase in DDD. Furthermore, 8 patients classified as absent success showed a decrease of SBP $\geq$20 mmHg, but were classified as absent clinical success because of an increase in DDD $\geq$50%. Nevertheless, in multiple patients it could be argued that the decrease in SBP surpasses the increase in absolute DDD value, and

therefore, these patients potentially should have been classified as partial success. Likewise, in 6 of the 16 patients with absent clinical success and an SBP increase ≥20 mmHg, the classification as absent success could be doubted because of large decrease in DDD (Supplementary Table II).

Discussion

This study examined the usefulness of the PASO consensus criteria for clinical outcomes after surgery for PA in a large cohort, which is representative for current clinical practice in multiple nations worldwide.[15] Our results showed complete, partial, and absent clinical success in 30%, 48%, and 22% of patients, respectively. These results indicate that when using the PASO consensus criteria, nearly 80% of patients benefit from surgery through clinically relevant decreases in blood pressure or antihypertensive medications, with subsequent expected decreases in morbidity, mortality, and potential drug-induced side effects.[20,24] Evaluation of the PASO criteria, however, showed that in 11% and 47% of patients with a partial and absent clinical success, this classification is potentially incorrect or debatable (16% of the total cohort). Our interpretation is that the PASO criteria have potential limitations, which mainly originate from the relatively high cutoff of ≥20 mmHg used to indicate a clinically relevant change in SBP and the fact that the change in DDD is expressed as a percentage instead of an absolute value. Therefore, this study showed that classifying clinical success after surgery for PA remains somewhat debatable, especially in patients with opposing changes in blood pressure and DDD.

Although many studies reported on the proportion of patients achieving clinical success after adrenalectomy for PA, the results of these studies varied widely because of the absence of uniform and standardized outcome criteria.[15–18] The PASO investigators introduced the first step toward a uniform and structured presentation of clinical outcomes by establishing a clear and feasible definition for partial clinical success.[15] Within our cohort, the proportion of patients with partial success was comparable with the 47% of patients presented by the PASO investigators, but fewer patients showed complete clinical success, and therefore more patients had absent clinical success, 30% vs 37% and 22% vs 16%, respectively. This greater rate of less favorable outcomes may be due to the somewhat greater baseline body mass index and DDD within our cohort compared with the PASO cohort, 30 ± 6 kg/m^2 vs 28 ± 5 kg/m^2 and 3.7 (IQR 1.8–5.5) vs 3.0 (IQR 1.5–4.7). Multiple studies also indicated female sex, age, duration of hypertension, and baseline SBP as predictors; however these characteristics were comparable between the 2 studies.[15,25–27] Similar to the PASO cohort, we showed a considerable heterogeneity in the proportions of patients with complete, partial, and absent clinical success among centers (Supplementary Fig). Therefore, participation of different medical centers and patient selection could also be of influence. Furthermore, because our cohort represents real-life clinical practice rather than a formal study protocol in a university center, the preoperative workup, including screening, case confirmation, and determining disease laterality, was not as stringent as in the PASO cohort.

This could be a limitation of this study, most importantly because AVS was not performed routinely. Although outcomes were comparable between patients with and without preoperative AVS, this could still be of influence to the lesser rates of complete success. For instance, because of confounding by indication, AVS might have been performed in cases with a greater risk of less favorable outcomes. Furthermore, because our cohort consisted of patients operated on between 2010 and 2016 compared with between 1995 and 2015 within the PASO cohort, the lesser rates of complete success could also be influenced by the worldwide increase in obesity and background or not PA-related hypertension through the years.[28,29]

In addition to clear criteria for clinical success, the PASO investigators also reached consensus on the timing of the final outcome assessment. They suggested that the final outcome assessment should be performed at 6 to 12 months after adrenalectomy. Unfortunately, the collection of data in our cohort was initiated before the publication of the PASO consensus, and therefore the timing of outcome assessment was already determined at follow-up closest to 6 months (range 3–9) after adrenalectomy. Because of geographic distances and referral patterns in daily clinical practice, multiple centers were not able to report follow-up within this timeframe. To prevent a high percentage of loss to follow-up, we chose to also include other follow-up durations. Although the timing of follow-up had no apparent significant influence on primary outcomes within our cohort, the substantial number of patients with a short follow-up (n = 86) remains a limitation of our study.

For use in day-to-day practice, the PASO criteria appeared to have some limitations when applied to our cohort. For instance, many patients achieved a 10 to 19 mmHg decrease in SBP with a substantial decrease in their absolute value of DDD. These patients clearly showed clinically relevant benefits from surgery and therefore, in our opinion, were incorrectly classified as absent success because the changes in SBP and DDD were <20 mmHg and <50%, respectively. Based on current literature, indicating a considerable decrease in cardiovascular morbidity and mortality for each 10 mmHg decrease in SBP in patients with hypertension, we believe this cutoff should be decreased to ≥10 mmHg.[20] In our opinion, 30% of the patients who were classified as absent success according to the PASO criteria (7% of the complete cohort) would have been classified more accurately as partial success when the cutoff was adjusted to ≥10 mmHg (Table IV). Moreover, this change in cutoff minimizes the risk of classifying patients as partial success, based on a decrease in DDD, despite a clinically relevant increase in SBP (eg, a 10 to 19 mmHg increase). Furthermore, the use of percentages, rather than absolute values, to indicate changes in DDD is also a potential drawback of the PASO criteria. Especially in patients with low- or high-preoperative DDD, our data showed discrepancies. For instance, a change in DDD from 1.0 to 0.5 and 6.0 to 3.0 both equal a 50% decrease, but most likely results in a different decrease in blood pressure. Evidence from studies performed in patients with essential hypertension suggests an average 9 mmHg decrease in the SBP at the standard dose (1 DDD) of a antihypertensive drug. Therefore, one could suggest a ≥1 DDD cutoff to indicate a change in antihypertensive medication, which equals the proposed ≥10 mmHg cutoff to indicate a change in SBP.[30] Determining the cutoff in DDD that equals the clinically relevant decrease in blood pressure, however, remains a major challenge because of the complex relationship between the change in DDD and blood pressure. This concept is particularly important because 2 drugs at half dose add up to 1 DDD, but the decrease in blood pressure has proven to be substantially more than for 1 drug at 1 DDD.[30] Furthermore, patients with twice the standard dose (2 DDD) of a antihypertensive drug only achieve a small additional decrease in SBP compared with patients on the standard dosage (1 DDD).[30] Likewise, in patients with PA, the use of 1 DDD of a mineralocorticoid receptor antagonist probably results in better blood pressure control compared with 1 DDD of a different antihypertensive drug.

Similar to the majority of studies regarding PA, the need for a retrospective design owing to the low incidence of PA is one of the weaknesses of our study. Because of this retrospective design, it was necessary to use office blood pressure measurements. These

measurements are prone to be affected by patients' change in blood pressure throughtout the day, instead of out-of-office 24-hour measurements that could be considered the new standard of care.[22,23] As mentioned earlier, not performing AVS in all patients, the substantial number of patients with relatively short follow-up (<1 month) after surgery regarding clinical outcomes, and not performing postoperative measurements of aldosterone in all patients are limitations of this study. These limitations, however, did not result in clear differences in our primary outcomes. Also, we believe that not performing AVS in all patients is an acceptable limitation for a cohort study based on real-life clinical practice and makes the results more generalizable to the overall management of PA worldwide because the preoperative workup differs globally.

In conclusion, the PASO investigators introduced a substantial advance for the study of postoperative outcomes in PA by the development of standardized clinical outcome criteria. Building on this consensus, our study shows that there may be room for improvement in the classification of success by exposing some of the potential limitations of the PASO criteria. We hope this study could inspire hypertension specialists, endocrinologists, and surgeons to join forces with the goal to further optimize and standardize the assessment of blood pressure-related outcomes after surgery for PA. This attempt to further standardize outcomes is important because only after establishing clear and valid outcome definitions is it possible to properly investigate the true prognostic and discriminating factors that could be used for patient counseling.

Conflicts of interest

The authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.01.031.

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