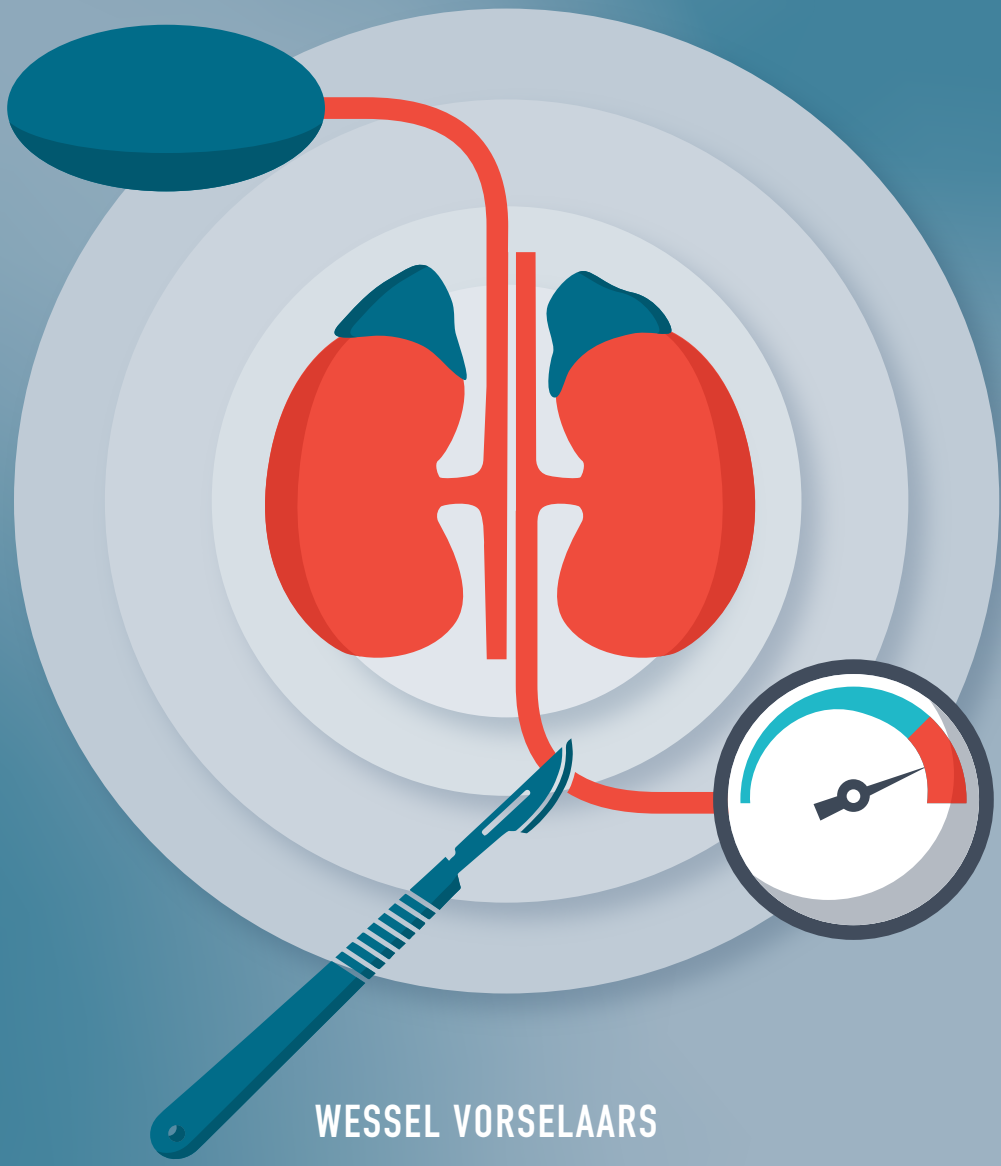
SURGICAL TREATMENT OF HYPERTENSION

Preoperative work-up and surgical treatment
of primary aldosteronism in current daily practice



WESSEL VORSELAARS

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Surgical treatment of hypertension
Preoperative work-up and surgical treatment of primary aldosteronism in current daily practice

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Preoperative work-up and surgical treatment of primary aldosteronism
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DE CHIRURGISCHE BEHANDELING VAN HYPERTENSIE

De preoperatieve work-up en de chirurgische behandeling van
primair hyperaldosteronisme in de hedendaagse praktijk

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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TABLE OF CONTENTS

APPENDICES

CHAPTER

1

General introduction & thesis outline

HYPERTENSION

Hypertension, also known as high or raised blood pressure, is a condition in which the arteries persistently bear a raised pressure and is defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg[1-3]. Globally, 1.1 billion people suffer from hypertension, which equals 22% of the worldwide adult population[4,5]. The World Health Organization indicates hypertension as a major public health issue, since 10 million people die from hypertension annually[6]. Besides the high risk of mortality, patients suffer from morbidity due to hypertension-related diseases such as heart disease, stroke and kidney failure. Hypertension itself rarely causes symptoms, therefore, many people still go undiagnosed making hypertension a silent and invisible killer[4]. The majority of patients have primary hypertension, which is often referred to as essential hypertension. Primary hypertension has no clear cause and is thought to be linked to people's behavior such as poor diet, smoking and lack of exercise. Secondary hypertension, on the other hand, is caused by an underlying condition of the kidneys, arteries, heart or endocrine system.

PRIMARY ALDOSTERONISM

Primary aldosteronism (PA), is the most common cause of secondary hypertension. Approximately half a century ago, PA was considered a very rare disease with an estimated prevalence below 1% in hypertensive patients[7,8]. In the following decades, accumulating evidence has overturned this assumption with a reported rise in the prevalence of PA, most likely due to better awareness and diagnosis of the disease. Although current literature is heterogeneous, the prevalence of PA is estimated to be above 5% in the general hypertensive population[9-12]. Assuming a prevalence of hypertension of 22% worldwide, this would imply that approximately 1 in every 100 individuals suffers from PA. Therefore PA should be considered a serious health issue[13,14].

As first described by Jerome Conn in 1955, PA is characterized by the excessive endogenous production of the mineralocorticoid hormone aldosterone by one or both of the adrenal glands. This production is inappropriate and autonomous of the renin-angiotensin system[15]. The aldosterone excess induces renal sodium and water retention with an increase in blood pressure as a result. This aldosterone excess is not only important because of the direct effect of hypertension on morbidity and mortality, but also because patients with PA have higher morbidity and mortality compared to patients with primary hypertension[14,16-18]. This is due to the elevated aldosterone levels which induce tissue inflammation and an increased central sympathetic drive leading to fibrosis and remodeling of critical organs, including the kidneys, heart and vessels. Therefore, PA contributes to diseases such as renal insufficiency, myocardial infarction, heart failure and stroke[14,16-18].

The classical presentation of PA is a patient with resistant hypertension, defined as failure to achieve a normal blood pressure despite an appropriate regimen of three or more antihypertensive medications, and hypokalemia, which is due to the increased renal sodium resorption with subsequent high potassium loss[15]. Nevertheless, PA has been described in patients with all degrees of hypertension and in patients with normal potassium levels[13].

SURGICAL TREATMENT OF PA

PA is commonly caused either by an aldosterone-producing adenoma (APA) (35 – 40%) or bilateral adrenal hyperplasia (BAH) (60 – 65%)[13,15,19]. APA is preferably treated surgically by performing a unilateral adrenalectomy and BAH is treated medically with a mineralocorticoid receptor antagonist (e.g., spironolactone or eplerenone)[13]. In surgery for PA, the laparoscopic adrenalectomy has become the standard treatment since first described by Gagner in 1992[20]. In current practice, the transabdominal and retroperitoneal approach are most frequently used. Because both procedures are minimal invasive, the morbidity rates are low and the duration of hospital stay is frequently less than a couple of days[21,22].

THESIS OUTLINE

Present literature lacks valid data on how we currently perform the work-up to surgery for PA and on what the precise benefits of surgery are. Therefore, this thesis is focused on the preoperative work-up and the benefits of surgery in patients treated for an APA in current daily clinical practice.

WORK-UP TO SURGERY

The Endocrine Society Guideline recommends screening for PA with the aldosterone-to-renin ratio (ARR) in patients with a relatively high risk of PA. More specifically, patients with resistant hypertension, hypertension and hypokalemia or hypertension and an adrenal incidentaloma on imaging should be screened[13]. Although the ARR is recommended and therefore widely used, valid estimations of the diagnostic accuracy of the ARR are scarce[13]. Missing a patient with PA may lead to unnecessary morbidity and mortality due to lifelong inadequate treatment of hypertension and aldosterone excess. Therefore, we aimed to evaluate the clinical consequences of screening with the ARR in patients with suspected PA by assessing the diagnostic accuracy in a prospective study in **chapter 2.**

According to the guidelines, a confirmatory test should be performed when screening for PA with the ARR is positive to rule out false positive ARR results and, thereby, establish the PA diagnosis[13]. If PA is diagnosed, a computed tomography (CT) scan is advised, mainly to exclude

rare cases of aldosterone producing adrenocortical carcinoma. Although CT can also display adrenal adenomas, adrenal venous sampling (AVS) is recommended as the most reliable modality for subtype testing (i.e., distinguishing the surgically treatable APA from BAH)[13]. Regarding this recommended work-up to adrenalectomy in patients with PA however, numerous controversies exist in literature[23,24]. Moreover, experts in the field of PA advocate conflicting work-up strategies and some diagnostic modalities, such as AVS, are expensive and technically demanding[23,24]. This might encourage clinicians to deviate from the guidelines in daily clinical practice, but data on this is lacking in current literature. Therefore, we investigated and displayed the performed surgical work-up in current daily clinical practice within an international cohort in **chapter 3**.

BENEFITS OF SURGERY

While BAH is treated medically, surgery is the cornerstone of APA treatment[13]. Since both hypertension and aldosteronism contribute independently to morbidity and mortality, the ultimate goal of surgery is curation of both[14,16-18]. Cure of aldosteronism (i.e., biochemical cure) is reported in the majority of patients after adrenalectomy for PA[25-27]. However, from a patient's perspective, the improvement in blood pressure control and a decrease in antihypertensive drug burden is more striking compared to biochemical cure and therefore patients could note this as the most important benefit of surgery.
Complete clinical success, also named clinical cure, is the state in which a patient becomes normotensive without the need for antihypertensive medications after surgery. Although results vary across studies, complete clinical success is no certainty and should be expected in ≤ 50% of patients[25-27]. Nevertheless, patients without complete clinical success may also benefit from surgery through a reduction of blood pressure and/or antihypertensive medications with a subsequent decrease in morbidity, mortality and drug burden. The decrease in blood pressure is very important, since every decrease of 10 mmHg in systolic blood pressure leads to a relative risk-reduction of 20% in major cardiovascular events and 13% in all-cause mortality in patients with hypertension[28,29]. This risk-reduction is shown across various baseline blood pressure levels and is therefore not associated with crossing the blood pressure threshold that currently defines hypertension[29]. In the past, multiple studies focused on presenting the proportion of patients with complete clinical success, but data on the decrease in blood pressure and antihypertensive medications was lacking. To achieve better understanding of the benefits of surgery in patients with PA, we set out to investigate and precisely display the effect of adrenalectomy on blood pressure and antihypertensive medications in **chapter 4**.

In 2017, the Primary Aldosteronism Surgical Outcome (PASO) Study Group was the first to classify the decrease in blood pressure and antihypertensive medications after surgery by introducing standardized outcome definitions based on a Delphi consensus. Clinical success was defined as either being complete, partial or absent based on a decrease in blood pressure and antihypertensive medications. In this stratification, patients with partial clinical response

are not completely cured, but still benefit from surgery through a significant and clinically relevant decrease in systolic blood pressure of ≥ 20 mmHg and/or decrease of ≥ 50% in their antihypertensive medications[25]. Patients without complete or partial clinical success are defined as absent clinical success, which implies that the operation did not result in clinical benefits. We hypothesized that these criteria might incorrectly classify patients as either partial or absent clinical success due to the relatively high cut off used to indicate a clinically relevant change in systolic blood pressure (i.e., ≥ 20 vs. ≥ 10 mmHg) and use of percentages instead of absolute values to implicate a change in antihypertensive medications. Therefore, we evaluated these consensus criteria within daily clinical practice in **chapter 5**.

As mentioned before, complete cure of hypertension after surgery is far from a certainty, thereby underscoring the need for preoperative patient counseling and expectation management. The Aldosteronoma Resolution Score (ARS) is a user-friendly prediction model, including only 4 variables, which could be used to predict cure of hypertension during patient counseling[30]. The model was developed in a United States population over a decade ago. Performance of prediction models may change over time due to, for instance, changes in patient characteristics or the effect of treatment strategies[31-33]. Therefore, we evaluated the clinical applicability and usefulness of the ARS in the current population of patients with PA in **chapter 6**.

INTERNATIONAL CONNSORTIUM STUDY GROUP

The International CONNsortium Study group is a collaboration between 16 medical centers from the United States, Canada, Australia and Europe and was originated by the University Medical Center Utrecht in 2016. The primary aim of this collaboration was to set up an international database with the goal to evaluate the work-up to and benefits of surgery for PA in current clinical practice. Retrospective data was collected from operated patients over the period 2010 – 2016. The obtained study cohort and data form the basis for **chapters 3 – 6** of this thesis. This is the first study cohort only including patients operated in recent years making it representative for current daily practice and, along with the PASO cohort, it is one of the leading databases in current literature[25].

RESEARCH AIMS PER CHAPTER

Chapter 2: To evaluate the diagnostic value of the ARR by using a standardized prospective study protocol, which is in line with the Endocrine Society Guideline recommendations regarding indications for screening, testing conditions and reference standards.
Chapter 3: To investigate and display the performed work-up to adrenalectomy for PA within current daily clinical practice.
Chapter 4: To examine and precisely describe the effect of adrenalectomy on blood pressure and antihypertensive medications and thereby giving better insight in the benefits of surgery for PA.
Chapter 5: To evaluate the PASO consensus criteria for clinical outcomes after surgery for PA within a cohort reflecting daily clinical practice.
Chapter 6: To validate the ARS within current PA population in the United States and extend this geographically to Canada, Australia and Europe.

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PART

1

PREOPERATIVE WORK-UP IN PRIMARY ALDOSTERONISM

CHAPTER

2

Case detection in primary aldosteronism: high diagnostic value of the aldosterone-to-renin ratio when performed under standardized conditions

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ABSTRACT

Objective

The aldosterone-to-renin ratio is widely used and the recommended screening modality for primary aldosteronism by the Endocrine Society Guideline. However, studies on its diagnostic accuracy have been inconsistent, which is mainly due to methodological limitations. We set out to evaluate this diagnostic value by using a highly standardized study protocol, which is in line with the Endocrine Society Guideline recommendations regarding indications for screening, testing conditions and reference standards in daily clinical practice.

Methods

In this prospective study, 233 consecutive patients referred to the University Medical Center Utrecht with difficult-to-control hypertension were enrolled. Besides aldosterone-to-renin ratio measurements all patients underwent a saline infusion test as a reference standard. A plasma aldosterone concentration >280 pmol/L after saline infusion was considered diagnostic for aldosteronism and the plasma renin activity was assessed to exclude patients with secondary aldosteronism from the final primary aldosteronism diagnosis.

Results

Correlation of the aldosterone-to-renin ratio (cut-off >5) with primary aldosteronism diagnosis showed 16 true positive, 29 false positive, 188 true negative and 0 false negative aldosterone-to-renin ratios, resulting in a sensitivity of 100.0% (CI 75.9 – 100.0), specificity of 86.7% (CI 81.2 – 90.7), positive-predictive-value of 35.6% (CI 22.3 – 51.3) and negative-predictive-value of 100.0% (CI 97.5 – 100.0). The corresponding area under the curve was 0.933 (CI 0.900 – 0.966).

Conclusions

These findings show that the aldosterone-to-renin ratio is a good screening modality for primary aldosteronism and is without a high risk of missing a primary aldosteronism diagnosis when performed under well standardized conditions.

INTRODUCTION

Primary aldosteronism (PA), first described by Jerome Conn in 1955, is the most commonly occurring type of endocrine hypertension[1]. In PA, the excessive endogenous production of aldosterone by one or both of the adrenal glands is partially or completely autonomous of the renin-angiotensin system[2,3]. Although aldosterone excess is directly linked to hypertension through renal sodium and water retention, aldosteronism itself also induces tissue inflammation and an increased central sympathetic drive, with subsequent fibrosis and remodeling in critical organs such as the kidney, heart, and vasculature[3-7]. Therefore, PA may lead to renal insufficiency, atrial fibrillation, stroke, and myocardial infarction[7-10]. In the last decades the prevalence of PA has risen, predominantly due to improved awareness and subsequent diagnosis. As a consequence, the recently published Endocrine Society Guideline (ESG) indicates PA as a major public health issue and stresses the importance of case finding as missing a PA diagnosis may lead to unacceptable risk for the patient[11].

To achieve accurate case detection the ESG recommends screening for PA with the aldosterone-to-renin ratio (ARR) in patients with relatively high risk of PA, and confirmation testing when the ARR is increased[11]. However, despite the fact that the ARR is recommended and therefore widely used, studies on its diagnostic accuracy have been inconsistent reporting sensitivities ranging from 22% to 100% and specificities from 61% to 100%[12-19]. This inconsistency could be explained by differences in cut-off values, laboratory assays, study populations, sampling conditions, and other methodological limitations[19-25]. In addition, in previous studies, the criteria used to confirm the PA diagnosis varied widely leading to different outcomes. On this basis, the recently published ESG states that valid estimations of the diagnostic accuracy of the ARR are still lacking[11].

With the aim to assess the clinical consequences of the ESG on PA, in a prospective study, we assessed the diagnostic value of the ARR as a screening test in patients who were consecutively referred to our institution because of difficult-to-control hypertension.

METHODS

Patients

We prospectively evaluated all consecutively referred patients with difficult-to-control hypertension to the department of Vascular Medicine of the University Medical Center Utrecht (Utrecht, The Netherlands), who underwent the local “Analysis of Complicated Hypertension” (ACH) protocol, between June 2015 and July 2017. The ACH is a highly standardized diagnostic protocol designed to diagnose or rule out secondary causes of hypertension (including PA), identify contributing factors of hypertension, and assess the overall cardiovascular risk profile in patients with difficult-to-control hypertension. Difficult-to-control hypertension was defined as persistent hypertension despite treatment according to the current guidelines and/or the presence of end-organ damage or vascular complications[26]. In general, patient selection for the ACH program was in line with the ESG criteria indicating patients with a relatively high risk

of PA (i.e., also taking hypokalemia, family history, incidentaloma and sleep apnea in to account)[11]. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and executed in accordance with the Good Clinical Practice guidelines. The need for written informed consent was waived by the Medical Ethics Committee.

Analysis of Complicated Hypertension (ACH) protocol

Our ACH protocol was described earlier[26]. All included patients underwent the analysis within the framework of the ACH protocol for which, after inclusion, all antihypertensive medication was temporarily withdrawn for at least two weeks. Six weeks prior to testing, mineralocorticoid receptor antagonists and renin inhibitors were stopped. Four weeks prior, β-blockers and central acting agents were tapered in two weeks. All other antihypertensives were stopped at once two weeks before testing. Patients were advised not to use NSAID's. During the screening period, protocolled dosages of diltiazem, verapamil or doxasozine could be used as escape medication, as they do not interfere with the biochemical evaluation of the ARR. Escape medication could be prescribed preventive at the start of the screening or at any time during the screening if considered necessary by the treating or on call hypertension specialist. Indications for escape medication included severe complaints and/or blood pressures >180/110 mmHg. As presented in one of our earlier studies, discontinuation of antihypertensive medication within our well-controlled ACH protocol does not increase the acute risk of cardiovascular events[26].

During the medication stop patients performed home blood pressure measurements (Watch BP© home, Microlife Europe, Widnau, Switzerland) two times a day. Patients were instructed to contact the hospital 24/7 in case of severe complaints and/or blood pressures >180/110 mmHg or when patients felt insecure or had any questions. The home blood pressure measurements were uploaded to a secure internet site and visible to the treating physicians of the hospital. During screening, 24-hr ambulatory blood pressure measurements (ABPM) (Watch BP© O3, Microlife Europe, Widnau, Switzerland) and office blood pressure measurements (OBPM) (Watch BP© home, Microlife Europe, Widnau, Switzerland) were performed before (at first presentation) and after withdrawal of hypertensive medication. OBPM were measured three times at both arms after at least five minutes in seated position. We considered the blood pressure measurements without medication as most representative for the severity of hypertension because possible influence of adequate/inadequate antihypertensive therapy was ruled out. Therefore, at least the OBPM without medication had to be performed in all patients.

Patient demographics and disease characteristics were collected. Number, types and dosages of antihypertensive medications at first presentation were recorded. Plasma aldosterone concentration (PAC; pmol/L) and plasma renin activity (PRA; fmol/L/s) before and after SIT were measured. The PAC and PRA before SIT were used to calculate the ARR. One week before testing (after one week without medication) serum potassium level was measured and in case of hypokalemia (<3.8 mmol/L) potassium supplementation was given to prevent false ARR or SIT results.

All patients underwent measurements of the ARR and the saline infusion test, regardless of

ARR outcome. Measurements were performed on out-patient basis with patients coming in early in the morning. Samples for PAC and PRA measurements were taken between 08.00-09.00 AM, after the patient has been up (sitting, standing, or walking) for at least two hours and seated for 5–15 minutes (upright position). This was followed by a PAC and PRA measurement in recumbent position after 2L saline infusion in four hours. During the last hour of the SIT the patient was instructed to stay in supine position. Calculation of the ARR was based on the PAC and PRA measurements before saline infusion.

Laboratory measurements

PRA was estimated from the conversion of angiotensinogen to angiotensin I in one hour at 37°C, under inhibition of the angiotensin-converting enzyme (ACE) by captopril and angiotensinase (A and B), by 8-OH quinoline and phenylmethylsulfonyl floride. Angiotensin I is measured using an in-house radioimmunoassay. Repeatability is 5.6 % at 90 fmol/L/s. Day-to-day coefficient of variance was 10.6% for a range of 190 – 4000 fmol/L/s. Reference range used was 150 – 1800 fmol/L/s in the upright position and 100 – 650 fmol/L/s in the supine position.

PAC was determined using the DPC Coat-a-Count radioimmunoassay (Siemens Healthcare Diagnostics Inc., Los Angeles, California, USA). Day-to-day coefficient of variance was 5.8% at 1450 pmol/L, 7.7% at 370 pmol/L and 20% at 50 pmol/L. Reference range used was 110 – 860 pmol/L in the upright position. Conversion of results from ICN to DPC radioimmunoassay is: [DPC aldosterone] = 1.45* [ICN aldosterone].

Serum potassium levels were measured using the AU 5711 Clinical Chemistry System (Beckman Coulter, Woerden, The Netherlands). Reference range used was 3.8 – 5.0 mmol/L.

Study outcomes

The primary outcome of this study is the diagnostic value (i.e. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC)) of the ARR for diagnosing PA. Furthermore, we report the prevalence of PA in our cohort with difficult-to-control hypertension. In accordance to the ESG, a PAC >280 pmol/L measured after 2L saline infusion in four hours is used as reference standard for diagnosing PA[11]. Since secondary/renin-driven aldosteronism could also lead to excessive secretion of aldosterone (PAC >280 pmol/L) after saline infusion a suppressed PRA was required for establishing the PA diagnosis. Thereby we excluded patients in which the aldosteronism was predominantly renin-driven and not of primary origin. In accordance with our laboratory reference values, unsuppressed PRA was defined as PRA >150 fmol/L/s in upright position (before SIT) and PRA >100 fmol/L/s in supine position (after SIT).

Statistical analysis

The diagnostic value of the ARR is presented as the sensitivity, specificity, PPV, NPV and AUC. At our institution an ARR >5 is the cut-off value used indicating a positive test. All continuous data are shown in mean values with standard deviation (± SD) unless indicated otherwise. Statistical analysis was performed using SPSS version 23.0 (Chicago, Illinois, USA).

TABLE 1 BASELINE CHARACTERISTICS

Variable	Cohort (n=233) June 2015 – July 2017
Age (years)	53.6 ± 13.4
Female	110 (47.2%)
Body mass index (kg/m^2)	27.8 ± 4.6
OBPM with medication (mmHg)(n=207)	
Systolic	165 ± 26
Diastolic	97 ± 14
ESH hypertension grade based on OBPM with medication	
Grade 0	21 (9.0%)
Grade 1	59 (25.3%)
Grade 2	54 (23.2%)
Grade 3	74 (31.3%)
No OBPM with medication performed	26 (11.2%)
ABPM with medication (mmHg)(n=198)	
Systolic	142 ± 17
Diastolic	85 ± 11
OBPM without medication (mmHg)	
Systolic	172 ± 25
Diastolic	100 ± 16
ABPM without medication (mmHg)(n=221)	
Systolic	153 ± 18
Diastolic	92 ± 12
No. of different classes of antihypertensives*	2 (0 – 6)
Used classes of antihypertensive at first presentation	
Calcium channel blocker	105 (45.1%)
Diuretics	84 (36.1%)
Beta blocker	86 (36.9%)
ACE inhibitor	75 (32.2%)
Angiotensin II antagonist	66 (28.3%)
Aldosterone antagonist	25 (10.7%)
Alpha blocker	17 (7.3%)
Renin inhibitor	8 (3.4%)
Central acting drug	4 (1.7%)
Vasodilator	2 (0.9%)
ACH protocol performed, including	
ARR	233 (100%)
Saline infusion	233 (100%)
Laboratory measurements	
PAC (pmol/L)*	490 (<70 – 3890)
PRA (fmol/L/s)*	280 (<40 – 9100)
ARR*	1.5 (0.2 – 53.8)
Need for escape medication	65 (27.9%)

* Values not normally distributed are given as median (range).
Abbreviations: OBPM = Office Blood Pressure Measurement; JNC = Joint National Commission; ESH = European Society of Hypertension; ABPM = 24-hour Ambulatory Blood Pressure Measurement; No. = Number; ACH = analysis of complicated hypertension; ARR = aldosterone-to-renin ratio; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

RESULTS

A total of 440 patients were referred with difficult-to-control hypertension to our institution. Of those patients, 233 (53.0%) patients were entered into the ACH. Baseline characteristics of these 233 patients are shown in Table 1. The population consisted of 110 (47.2%) females and the mean age was 53.6 (± 13.4) years. Based on the OBPM with medication, grade three hypertension was most frequent (31.3%). During the medication stop 65 (27.9%) patients used escape medication. The mean 24-hr ABPM without medication was 153 (±18)/ 92 (±12) mmHg. The median PAC was 490 (<70 – 3890) pmol/L and PRA was 280 (<40 – 9100) fmol/L/s. The corresponding median ARR was 1.5 (0.2 – 53.8).

Prevalence of primary aldosteronism

From the 233 patients who underwent the ACH protocol 26 (12.2%) patients had a positive SIT indicating excessive secretion of aldosterone. Descriptive case presentation of these patients with a PAC >280 pmol/L after SIT is shown in Table 2. Ten of these patients had unsuppressed PRA before and after SIT indicating that the aldosteronism was (primarily) renin-driven. Sixteen patients had aldosteronism combined with suppressed PRA confirming the PA diagnosis. Based on these criteria, the prevalence of PA was 3.6% (16/440 patients) in the total population referred to our institution with difficult-to-control hypertension and 6.9% (16/233 patients) in the population who underwent the ACH protocol. Further work-up, treatment and follow-up of the 16 patients with the PA diagnosis is shown in Table 3.

Diagnostic accuracy of the aldosterone-to-renin ratio

Correlation of the ARR (>5) outcome with the PA diagnoses resulted in 16 true positive, 29 false positive, 188 true negative and 0 false negative ARR outcomes, resulting in a sensitivity of 100.0% (CI 75.9 – 100.0), specificity of 86.7% (CI 81.2 – 90.7), PPV of 35.6% (CI 22.3 – 51.3) and NPV of 100.0% (CI 97.5 – 100.0). The corresponding AUC was .933 (CI .900 – .966). The diagnostic value for multiple other ARR cut-off points, ranging van >2 to >10, is shown in Table 4.

DISCUSSION

In our study the ARR turned out to have an excellent diagnostic accuracy (i.e., sensitivity 100.0%, specificity 86.7%, PPV 35.6%, NPV 100.0% and AUC .933) when screening was performed using a well standardized protocol. Therefore, our results support the recommendation from the ESG to screen for PA with the ARR and to perform a confirmatory test only in case of a positive ARR[11].

This study prospectively investigated the diagnostic value of the ARR using a well standardized protocol which is in line with the ESG recommendations regarding the indications for screening, the ARR testing conditions and reference standards[11]. The main limitation of

TABLE 2 DESCRIPTIVE PRESENTATION OF ALL 26 CASES WITH PAC >280 PMOL/L AFTER SIT

Gender	Age	PAC*	PRA*	ARR	PAC after SIT	PRA after SIT*	eGFR*	Diagnoses
Female	55	2960	9100	0.33	450	5500	69	*Renin-driven aldosteronism*
Female	28	730	2100	0.35	340	1000	90	*Renin-driven aldosteronism*
Male	47	1190	2500	0.48	450	1200	85	*Renin-driven aldosteronism*
Female	52	520	990	0.53	670	740	84	*Renin-driven aldosteronism*
Male	35	1040	1100	0.95	410	560	56	*Renin-driven aldosteronism*
Male	50	950	1000	0.95	340	400	57	*Renin-driven aldosteronism*
Female	57	1310	1000	1.31	350	530	>90	*Renin-driven aldosteronism*
Male	43	470	280	1.68	380	280	69	*Renin-driven aldosteronism*
Male	43	3100	1200	2.58	800	370	80	*Renin-driven aldosteronism*
Male	47	920	330	2.79	640	180	78	*Renin-driven aldosteronism*
Male	50	1250	170	7.35	300	62	81	*Primary aldosteronism*
Male	55	1530	190	8.05	310	99	90	*Primary aldosteronism*
Male	60	1000	130	7.69	680	81	90	*Primary aldosteronism*
Male	60	590	40	14.75	320	40	75	*Primary aldosteronism*
Female	49	1580	90	17.56	1860	55	>90	*Primary aldosteronism*
Male	36	720	<40	18.00	310	<40	>90	*Primary aldosteronism*
Male	68	1040	<40	26.00	310	<40	64	*Primary aldosteronism*
Male	51	1070	<40	26.75	500	<40	>90	*Primary aldosteronism*
Male	54	1280	43	29.77	1180	<40	>90	*Primary aldosteronism*
Male	59	1590	44	36.14	1350	<40	>90	*Primary aldosteronism*
Male	56	1450	40	36.25	400	47	88	*Primary aldosteronism*
Male	73	1460	40	36.50	520	<40	71	*Primary aldosteronism*
Male	50	3890	100	38.90	760	64	>90	*Primary aldosteronism*
Female	70	1590	40	39.75	360	<40	36	*Primary aldosteronism*
Female	57	1840	<40	46.00	560	<40	>90	*Primary aldosteronism*
Male	49	2150	40	53.75	1560	<40	>90	*Primary aldosteronism*

* Reference range: PAC = 110 – 860 pmol/L(upright); PRA =150 – 1800 fmol/L/s(upright); PRA = 100 - 650 fmol/L/s(supine); eGFR = >90 ml/min/1.72m^2.
Legend: ARR >5 is the cut-off value used indicating a positive test. PAC >280 pmol/L after SIT was used as reference standard indicating aldosteronism. PRA >150 fmol/L/s before SIT and PRA >100 fmol/L/s after SIT was used to rule out renin-driven aldosteronism.
Abbreviations: PAC = plasma aldosterone concentration; PRA = plasma renin activity; ARR = aldosterone to renin ratio; SIT = saline infusion test; eGFR = estimated glomerular filtration rate.

previous studies assessing the diagnostic value of the ARR was that these studies did not perform a valid and standardized confirmatory test in all patients. Instead, in all or a subset of patients they based their PA diagnosis on a combination of other criteria such as regular PAC and PRA levels, imaging results, adrenal venous sampling, histology and clinical or hormonal improvement after surgery[12-19]. Therefore, in these studies, differential-verification bias could have led to invalid and/or difficult to interpret outcomes with regard to disease presence or absence[27].[27]

Up to now, the diagnostic accuracy of the ARR is in debate and valid estimations of the diagnostic accuracy, under the by the ESG recommended screening protocol, were lacking.

TABLE 3 WORK-UP, TREATMENT AND FOLLOW-UP OF THE 16 CASES DIAGNOSED AS PRIMARY ALDOSTERONISM

Gender	Age	PAC*	PRA*	ARR	PAC after SIT	PRA after SIT*	AVS	Treatment	Pathology	Clinical response
Male	50	1250	170	7.35	300	62	Unilat	Surgery	Adenoma	Improvement of HT
Male	55	1530	190	8.05	310	99	Bilat	Surgery	Adenoma	Persistent HT
Male	60	1000	130	7.69	680	81	NA	NA	NA	Waiting for AVS
Male	60	590	40	14.75	320	40	Unilat	Surgery	Adenoma/ hyperplasia	Improvement of HT
Female	49	1580	90	17.56	1860	55	Unilat	Surgery	Adenoma	Improvement of HT
Male	36	720	<40	18.00	310	<40	No	MRA	NA	Improvement of HT
Male	68	1040	<40	26.00	310	<40	No	MRA	NA	Improvement of HT
Male	51	1070	<40	26.75	500	<40	Unilat	Surgery	Adenoma	Improvement of HT
Male	54	1280	43	29.77	1180	<40	Unilat	Surgery	Adenoma	Improvement of HT
Male	59	1590	44	36.14	1350	<40	Unilat	Surgery	Adenoma	Improvement of HT
Male	56	1450	40	36.25	400	47	Unilat	Surgery	Adenoma	Cure of HT
Male	73	1460	40	36.50	520	<40	Bilat	MRA	NA	Improvement of HT
Male	50	3890	100	38.90	760	64	NA**	MRA	NA	Improvement of HT
Female	70	1590	40	39.75	360	<40	Unilat	Surgery	Adenoma	Improvement of HT
Female	57	1840	<40	46.00	560	<40	Unilat	Surgery	Adenoma	Improvement of HT
Male	49	2150	40	53.75	1560	<40	Unilat	Surgery	Hyperplasia	Cure of HT

* Reference range: PAC = 110 – 860 pmol/L(upright); PRA =150 – 1800 fmol/L/s(upright); PRA = 100 - 650 fmol/L/s(supine); eGFR = >90 ml/min/1.72m^2.

** The patient prefered treatment with MRA over surgery and therefore subtype classification with AVS was not performed.

Legend: Clinical response to therapy was assessed by a hypertension specialist during follow-up based on blood pressure and need for antihypertensive medications. The patient with persistent HT remained hypertensive after surgery unless optimal treatment with antihypertensive medications. Patients with improvement of HT became normotensive after introduction of MRA and normotensive with lower or equal antihypertensive medications when surgery was performed. Cure of HT was defined as a normotensive patients without the need of antihypertensive medications after surgery. Data regarding follow-up was retrospectively collected. Therefore, the moment of follow-up and measurements taken during follow-up were not standardized for this study.

Abbreviations: PAC = plasma aldosterone concentration; PRA = plasma renin activity; ARR = aldosterone to renin ratio; SIT = saline infusion test; AVS = Adrenal Venous Sampling; Unilat = Unilateral; HT = Hypertension; Bilat = Bilateral; NA = Not Applicable; MRA = Mineralocorticoid receptor antagonist.

Only two studies performed a confirmatory test recommended by the ESG in all patients to establish the PA diagnosis. Schwartz *et al.* showed 87% sensitivity and 75% specificity of the ARR and performed an oral salt loading test in all participants as confirmatory test[14]. However, by excluding patients with suspect secondary hypertension, unexplained hypokalemia and >3 antihypertensive drugs patients with a high risk for PA were excluded. Jansen *et al.* presented 22% sensitivity and 99% specificity[18]. However, they most likely underestimated the diagnostic value by using a lower PAC cut-off (≥235 pmol/L) after SIT as the reference standard indicating PA and not taking the PRA into account to exclude secondary aldosteronism from PA diagnosis.

Also, the reported prevalence of PA varies considerably between studies mainly due to differences in patient selection and criteria for PA diagnosis. Within an unselected population

TABLE 4 DIAGNOSTIC VALUE OF THE ALDOSTERONE TO RENIN RATIO AS SCREENING TEST FOR PRIMARY ALDOSTERONISM

Cut-off value	TP (n=)	FP (n=)	TN (n=)	FN (n=)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
ARR > 2	16	78	139	0	100.0% (75.9 – 100.0)	64.0% (57.2 – 70.4)	17.0% (10.3 – 26.5)	100.0% (96.7 – 100.0)	.820 (.756 – .885)
ARR > 3	16	52	165	0	100.0% (75.9 – 100.0)	76.0% (64.5 – 76.5)	23.5% (14.4 – 35.6)	100.0% (97.2 – 100.0)	.880 (.832 – .929)
ARR > 4	16	38	179	0	100.0% (75.9 – 100.0)	82.5% (76.7 – 87.2)	29.6% (18.4 – 43.8)	100.0 (97.4 – 100.0)	.912 (.873 – .952)
ARR > 5	**16**	**29**	**188**	**0**	**100.0% (75.9 – 100.0)**	**86.7% (81.2 – 90.7)**	**35.6% (22.3 – 51.3)**	**100.0% (97.5 – 100.0)**	**.933 (.900 – .966)**
ARR > 6	16	26	191	0	100.0% (75.9 – 100.0)	88.0% (82.8 – 91.9)	38.1% (24.0 – 54.4)	100.0% (97.5 – 100.0)	.940 (.909 – .971)
ARR > 7	16	23	194	0	100.0% (75.9 – 100.0)	89.4% (84.3 – 93.0)	41.0% (26.0 – 57.8)	100.0% (97.6 – 100.0)	.947 (.918 – .976)
ARR > 8	14	22	195	2	87.5% (60.4 – 97.8)	89.9% (84.9 – 93.4)	38.9% (23.6 – 56.5)	99.0% (96.0 – 99.8)	.887 (.790 – .983)
ARR > 9	13	15	202	3	81.3% (53.7 – 95.0)	93.1% (88.6 – 95.9)	46.4% (28.0 – 65.8)	98.5% (95.4 – 99.6)	.872 (.758 – .985)
ARR > 10	13	13	204	3	81.3% (53.7 – 95.0)	94.0% (89.7 – 96.7)	50.0% (30.4 – 69.6)	98.6% (95.5 – 99.60	.876 (.763 – .990)

Legend: In the University Medical Center Utrecht, ARR >5 is the cut-off value used indicating a positive test. PAC >280 pmol/L after saline infusion was used as reference standard indicating aldosteronism. For establishing the primary aldosteronism diagnosis also the plasma renin activity was taken in to account to exclude patients in which the aldosteronism was renin-driven and therefore of secondary origin.

Abbreviations: ARR = aldosterone to renin ratio; TP = true positive; FP = false positive; TN = true negative; FN = false negative; PPV = positive predictive value; NPV = negative predictive value; AUC = Area under the curve; CI = confidence interval; PAC = plasma aldosterone concentration.

of hypertensive patients prevalence is ranging from 4% to 18 % and within a selective population, only including patients with severe resistant hypertension, the reported prevalence is even higher, up to 29%[4,28-32]. Our results showed 3.6% prevalence in the total population referred to our institution with difficult-to-control hypertension. This is slightly lower compared to the two other studies using a similar PAC cut-off after SIT (PAC >277 pmol/L) to establish PA diagnosis, presenting a prevalence of 4.6% and 5.0%, respectively[4,28]. Most likely these differences are due to patient selection. For example, within our own cohort the prevalence of PA was higher (6.9%) within the population who underwent the ACH protocol due to the use of inclusion criteria selecting patients with a relatively higher risk of PA. Thus the prevalence of PA found in any population studied will depend strongly on the criteria employed to select patients for inclusion.

Since we already performed the ARR measurements on a standardized and out-patient basis for many years we were able to easily implement the SIT in general practice. This made it possible to prospectively investigate the diagnostic value of the ARR in all patients under the same and strictly controlled conditions. Moreover, this work-up, in which ARR measurements and SIT are performed on the same day, has logistical benefits such as reduction of delay in diagnosis due to a shorter work-up period and the need to only perform a medication stop once.

Currently four confirmatory tests (i.e., oral sodium challenge, SIT, fludrocortisone suppression test and captopril challenge) are in common use and recommended by the ESG. Though, current literature shows insufficient evidence to recommend one over the other making it hard to identify one 'gold standard' confirmatory test for PA[11]. However, also other potential diagnostic criteria such as pathology and clinical/biochemical cure after surgery, do not result in a 100% sure diagnosis especially since only patients with unilateral adrenal adenoma undergo surgery. Therefore, the absence of a clear 'gold standard' test to establish the PA diagnosis is a possible limitation of this study. However, in contrast to the majority of earlier performed studies, we used the same criteria to establish the PA diagnosis (i.e., positive SIT and suppressed PRA) in all patients, thereby excluding the influence of differential-verification bias. Moreover, we performed a confirmatory test in all patients, regardless of ARR outcome, thereby strongly reducing the potential influence of verification bias.

The reasonably low prevalence of this disease combined with a moderate sample size resulted in relatively wide confidence intervals, especially for sensitivity because this was based on only 16 cases with PA diagnoses. As a result, multiple ARR cut-offs (Table 4) had overlapping confidence intervals indicating non-significant differences. Therefore, the sample size could be a possible limitation of our study. Also, since our study was performed on out-patient basis with a well standardized sampling protocol including an adequate medication stop we should be careful with extrapolating these results to other institutions using less standardized protocols. Consequently, another possible limitation could be the external validity of our results.

Since the goal of screening is to detect patients with a specific disease and to safely rule out patients without the disease, a high sensitivity and NPV are the most important features for a screening test. Within our population no patients in whom PA was diagnosed would have

been missed when the screening only was performed with the ARR, resulting in a high sensitivity and NPV. Therefore, we can presume that the ARR is good screening modality and relying on it is without a high risk of missing a PA diagnosis. On the other hand, within the total population, 45 patients (19.3%) had a positive ARR and in 29 (12.4%) patients the ARR was false positive. In general practice this would imply that approximately 12% of patients who underwent screening for PA with the ARR will unnecessary undergo a SIT due to a false positive ARR. However, since the SIT is a relatively harmless and minimal invasive diagnostic procedure we believe that this is reasonable compared to the possible benefits of accurate case detection in PA.

This study illustrates the ARR as a good screening modality for PA when performed on out-patient basis under well standardized conditions. These results support the recommendation made by the ESG to screen for PA with the ARR and to perform a confirmatory test in case of a positive ARR. However, since the ARR is known to be influenced by multiple factors (i.e., cut-off values, laboratory assays, medication, sampling conditions, etc.) and medical centers worldwide show a large variety in diagnostic work-up protocols, which are not always well standardized, one could suppose that we still underdiagnose PA. We hope this study could instigate better standardization of diagnostic protocols and future research with the goal to optimize screening and diagnosis of PA.

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CHAPTER

3

Adrenalectomy for primary aldosteronism: significant variability in work-up strategies and low guideline adherence in worldwide daily clinical practice

SUBMITTED

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ABSTRACT

Background

Multiple controversies exist in the literature regarding the work-up for primary aldosteronism (PA) and various diagnostic tests and imaging modalities are available to establish the diagnosis and to determine laterality of disease. Within this multicenter retrospective cohort study we investigated the work-up before surgery for PA in daily clinical practice. We hypothesized that there would be low guideline adherence.

Methods

Patients who underwent unilateral adrenalectomy for PA within 16 centers in Europe, Canada, Australia and the United States between 2010 and 2016 were included. We did not exclude patients based on the performed diagnostic tests during work-up to make our data representative for current clinical practice. We analyzed adherence to the Endocrine Society Guideline and performed multivariable logistic regression to analyze variables associated with not performing adrenal venous sampling (AVS).

Results

In total, 435 patients were eligible. An aldosterone-to-renin ratio, confirmatory test, computed tomography (CT), magnetic resonance imaging and AVS were performed in 82.9%, 32.9%, 86.9%, 17.0% and 65.3% of patients, respectively. A complete work-up, as recommended by the guideline, was performed in 13.1% of patients. Bilateral disease or normal adrenal anatomy on CT (OR 16.19; CI 3.50 – 74.99), smaller tumor size on CT (OR 0.06; CI 0.04 – 0.08) and presence of hypokalemia (OR 2.00; CI 1.19 – 3.32) were independently associated with performing AVS.

Conclusion

This study is the first to examine the daily clinical practice work-up of PA within a worldwide cohort. Results demonstrate significant variability in work-up strategies and low adherence to The Endocrine Society guideline.

INTRODUCTION

Primary aldosteronism (PA) is the most common surgically treatable cause of secondary hypertension with an estimated prevalence of 5 – 20% within the hypertensive population[1-7]. In the vast majority of cases, PA is either caused by bilateral adrenal hyperplasia or by a unilateral aldosterone-producing adenoma (APA). While bilateral hyperplasia is generally treated with a mineralocorticoid receptor agonist, adrenalectomy is the preferred treatment for patients with APA[8,9]. In 2008, The Endocrine Society published a clinical practice guideline on PA with the goal of improving screening, work-up and treatment of PA worldwide[8]. The guideline recommended the use of the aldosterone-to-renin ratio (ARR) to detect cases of PA among hypertensive patients. Due to the risk of false positive ARRs, case confirmation with a confirmatory test was recommended in all patients with a positive ARR. Computed tomography (CT) was recommended to exclude adrenocortical carcinoma and in case surgery for PA was indicated, adrenal venous sampling (AVS) was recommended in all patients to distinguish APA from bilateral hyperplasia[8].
Within the work-up to adrenalectomy in patients with PA, however, a large variety of diagnostic tests and imaging modalities are available to establish the PA diagnosis and to determine laterality of disease. This is reflected in the numerous controversies in literature and between experts in the field regarding the different preoperative work-up strategies. Currently, the most important topic of discussion is whether all patients should undergo confirmatory testing and AVS[10-12]. In 2016, an update of the Endocrine Society Guideline was published[9]. This revised guideline suggested that a specific subgroup of patients potentially do not have to undergo confirmatory testing or AVS. However, these recommendations were based on a relatively low level of evidence[9]. We believe that the above mentioned illustrates the lack of convincing evidence regarding the best work-up to surgery in PA. Therefore, we hypothesized that clinicians might deviate from the Endocrine Society guideline within current daily clinical practice.

In the past, complete cure of hypertension after the operation was estimated in approximately 50% of patients[13,14]. However, recently the PASO study group and our own study group showed less optimistic results by presenting a 27 – 37% cure rate within large, international and well-executed studies[12,15,16]. This stresses the need to evaluate current practice with the goal to improve the benefits of surgery. Because present literature lacks data on how the work-up to surgery is performed in daily practice, we set out to evaluate and describe the performed work-up within a worldwide cohort of unselected patients who underwent unilateral adrenalectomy for PA between 2010 and 2016.

METHODS

Study population
We performed an international retrospective cohort study across 16 referral medical centers in Europe, Canada, Australia and the United States. The study cohort was established by the

International CONNsortium study group and the derivation of the cohort and the blood pressure related outcomes has been described in previous publications[15,16]. In brief, all consecutive patients who underwent unilateral total adrenalectomy for APA between 2010 and 2016 were included. Unilateral disease was diagnosed based on CT and/or magnetic resonance imaging (MRI) and/or AVS according to the preference and/or availability of these modalities within each medical center. Since the cohort was initiated for a different study aim (i.e., to describe the reduction of blood pressure and antihypertensive medications after adrenalectomy), patients with missing preoperative or follow-up data regarding systolic blood pressure (SBP), diastolic blood pressure (DBP) or corresponding number of antihypertensive medications were not included in the cohort[15,16]. Data collection was performed separately within each center with the use of a standardized data-entry-manual. Patient demographics, disease characteristics, laboratory data (e.g., measurements of ARR and confirmatory testing), results of CT/MRI/AVS, operative characteristics, pathology diagnosis and timing of follow-up were collected. Institutional review board approval was obtained in all participating centers.

Outcomes

The primary aim of this study was to evaluate the adherence to The Endocrine Society guideline for the work up of patients treated for PA[8]. As our cohort consisted of patients who had an adrenalectomy before (or around) publication of the most recent 2016 version of the guideline we chose to primarily compare our results to the guideline which was published in 2008[8]. Within the new 2016 guideline only two recommendations regarding work-up were introduced:

I. In case of hypokalemia, plasma renin levels below detection levels and aldosterone above >20ng/dL (550pmol/L) no confirmatory testing may be needed.
II. In case of age < 35 years old, hypokalemia, marked aldosterone excess and unilateral cortical adenoma on CT no AVS may be needed[9].

We additionally aimed to evaluate the potential influence of these new recommendations on clinical practice by examining the proportions of patients fulfilling/meeting these criteria within our cohort.

The secondary aim of this study was to identify potential disease or patient characteristics which encouraged clinicians to distinguish APA from bilateral hyperplasia and to determine laterality of disease based on CT alone without performing AVS.

Definitions

Due to the different assays and reference values within the participating centers we were not able to analyze absolute values of biochemical measurements. To compare laboratory data between the centers, measurements were classified as elevated or suppressed when they were above the upper or below the lower limit of the center's local reference ranges, respectively. Marked aldosterone excess was defined as an elevated aldosterone level and hypokalemia was defined as either a potassium level below the local reference range or the use of potassium supplementation. When results of biochemical measurements (e.g., ARR or confirmatory test) were not known within the operating centers, the measurement was

reported as not performed. When these measurements were performed in other medical centers before referral, results were reported within the database.

Statistical Analysis

Normally and not normally distributed continuous data are shown as mean (± standard deviation) and median (range). To compare continuous variables between groups, the Mann-Whitney *U* Test was used for not normally distributed data and independent samples t-tests for normally distributed data. The Chi-Square test and Fisher's exact test were used to analyze group differences for categorical variables. To analyze potential variables associated with not making use of AVS we performed multivariable logistic regression with backward stepwise selection including variables with $p<0.25$ in univariable analysis. Only patients who underwent CT were included in this analysis. Multiple potential prognostic variables had missing values. These variables were imputed using multiple imputation generating 20 imputed datasets[17]. Outcomes were not imputed. Pooled odds ratios with 95% confidence intervals were obtained from multivariable logistic regression. All tests were two-sided and p-values <0.05 were considered significant. Statistical analysis was performed using SPSS version 23.0 (Chicago, Illinois, USA) and figures were constructed using Graphpad Prism version 7.02 (GraphPad Software Inc, California, USA) and Draw.io version 10.5-1 (JGraph Ltd, Northamptonshire, UK).

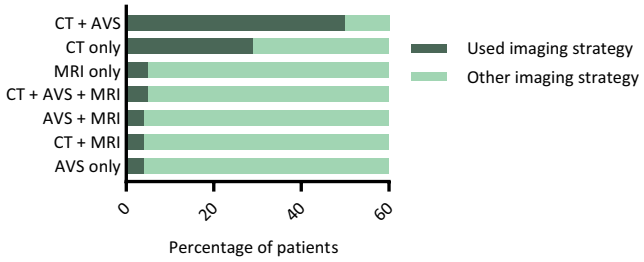
RESULTS

Four hundred and thirty-five patients were eligible for analysis. Baseline characteristics of these patients are presented in Table 1. Most patients were men (57.2%). The mean age and mean BMI were 50.7 ± 11.4 years and 29.7 ± 6.0 kg/m^2, respectively. Hypokalemia was present in 73.9% of patients and most patients had grade 1 hypertension (41.4%).

Preoperative work-up data of these patients are presented in Table 2. In 82.9% of patients a complete measurement of the ARR was performed and in 94.5% of these patients the ARR was elevated indicating PA. A confirmatory test was performed in 32.9% of all patients, indicating PA in 89.5%. CT, MRI and AVS were performed in 86.9%, 17.0% and 65.3% of the cohort, respectively. Almost half of the patients (49.9%) underwent both CT and AVS for subtype testing. CT only, MRI only and AVS only were used in 28.5%, 5.1% and 3.7% of patients, respectively. Furthermore, CT combined with MRI was used in 3.9% and MRI combined with AVS in 4.4% of patients. All 3 modalities were used in 4.6% of patients (Figure 1).

As indicated in Figure 2, large variability in work-up strategies was observed between the different medical centers. Depending on the medical center, the use of a confirmatory test, CT and AVS ranged from 0.0% to 94.6%, 66.7% to 100.0% and 9.1% to 100.0% of patients, respectively. All centers used AVS in some cases and only 1 center performed AVS in all cases. Furthermore, MRI was used in all medical centers except one.

FIGURE 1 IMAGING MODALITIES USED FOR SUBTYPE TESTING.



Abbreviations: CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; AVS = Adrenal Venous Sampling

TABLE 1 BASELINE CHARACTERISTICS OF 435 PATIENTS

Variable	Number (%) or mean ± SD
Age at surgery (years)	50.7 ± 11.4
Female	186 (42.8%)
Duration of hypertension (years)(n=366)*	9 (0 – 42)
Body mass index (kg/m^2)(n=402)	29.7 ± 6.0
Number of antihypertensive medications	3 (0 – 8)
Defined daily dose (n=405)*	3.7 (0.0 – 25.3)
Hypokalemia (n=429)	317 (73.9%)
Preoperative mean SBP (mmHg)	150 ± 20
Preoperative mean DBP (mmHg)	90 ± 13
JNC/ESH hypertension grade based on blood pressure with medication	
Grade 0	111 (25.5%)
Grade 1	180 (41.4%)
Grade 2	105 (24.1%)
Grade 3	39 (9.0%)
Surgical procedure	
EPRA	171 (39.3%)
ELRA	65 (14.9%)
LTA	198 (45.5%)
Open	1 (0.2%)

* Values not normally distributed given as medians (range)
Abbreviations: JNC = Joint National Commission; ESH = European Society of Hypertension; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; EPRA = Endoscopic Posterior Retroperitoneal Adrenalectomy; ELRA = Endoscopic Lateral Retroperitoneal Adrenalectomy; LTA = Laparoscopic Transabdominal Adrenalectomy.

Adherence to the 2008 Endocrine Society Guideline

Out of the 435 patients who underwent surgery for PA, screening was performed by a complete ARR in 361 patients (83.0%) and in 341 patients (78.4%) this ARR was elevated suggesting PA (Figure 3). Of the patients without a preoperative ARR, a preoperative aldosterone measurement was performed in 63.5% of patients showing elevated aldosterone levels in 72.3% of these patients. A confirmatory test was performed in 114 of the 341 patients with

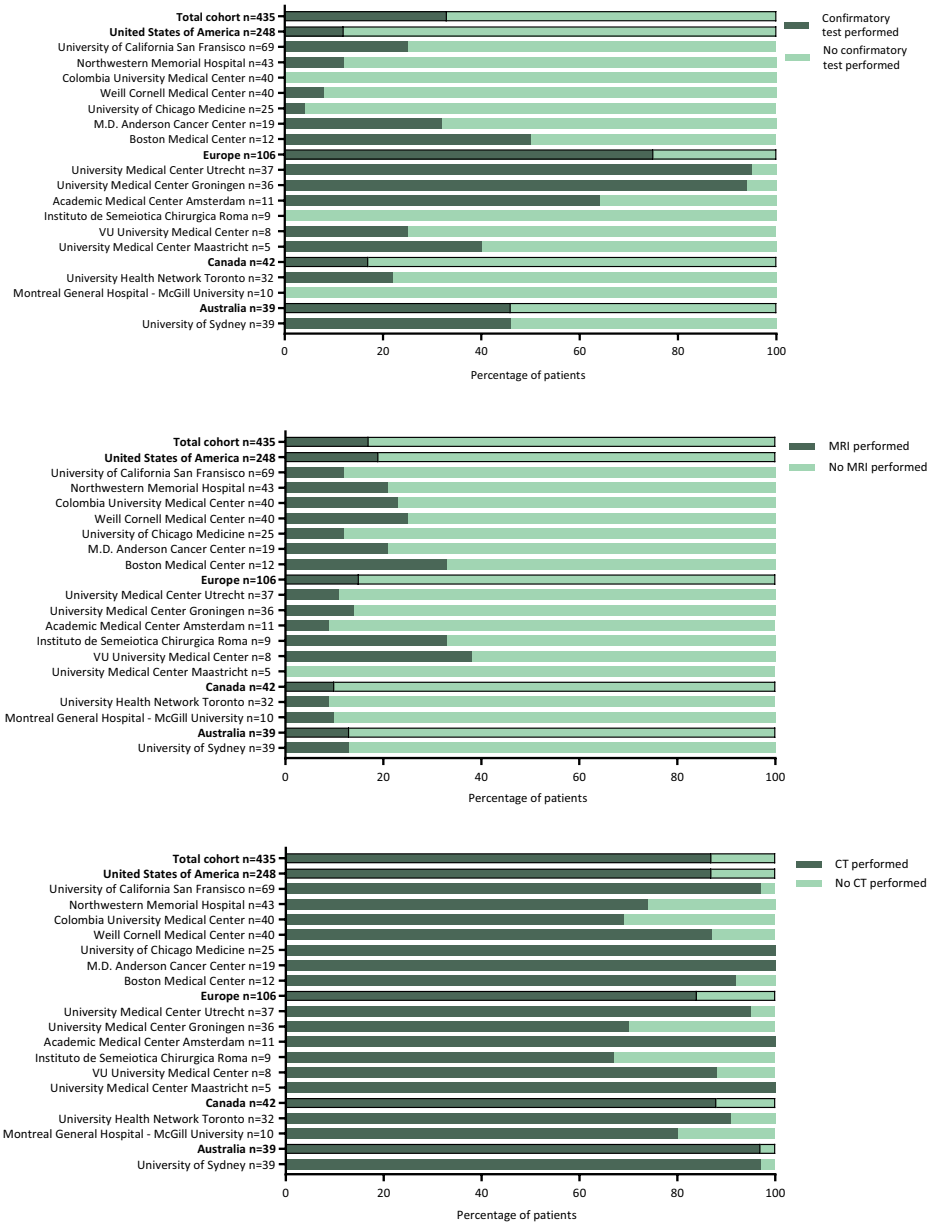
TABLE 2 PREOPERATIVE WORK-UP

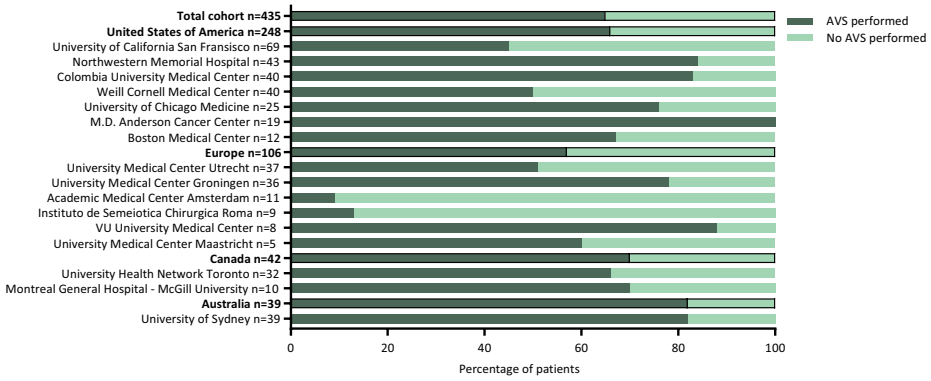
Variable	Number (%)
Measurement of aldosterone performed	408 (93.8%)
Aldosterone elevated	225 (55.1%)
Measurement of renin performed	370 (85.1%)
Renin suppressed	245 (66.2%)
Measurement of ARR performed	361 (82.9%)
ARR elevated	341 (94.5%)
Confirmatory test performed	143 (32.9%)
Oral salt loading	18 (12.6%)
Saline infusion test	118 (82.5%)
Fludrocortisone suppression test	3 (2.1%)
Captopril challenge	1 (0.7%)
Fludrocortisone dexamethasone suppression test	1 (0.7%)
Post-low dose dexamethasone suppression – saline infusion test	1 (0.7%)
Confirmatory test indicating PA	
Yes	128 (89.5%)
No	13 (9.1%)
Missing data	2 (1.4%)
CT performed	378 (86.9%)
Unilateral disease	325 (86.0%)
Bilateral disease	28 (7.4%)
Normal adrenal anatomy	21 (5.6%)
Missing data	4 (1.1%)
MRI performed	72 (17%)
Unilateral disease	63 (87.5%)
Bilateral disease	3 (4.2%)
Normal adrenal anatomy	5 (6.9%)
Missing data	1 (1.9%)
AVS performed	284 (65.3%)
Unilateral disease	263 (92.6%)
Bilateral disease	7 (2.5%)
No lateralization	7 (2.5%)
Failure of procedure	6 (2.1%)
Missing data	1 (0.4%)

Abbreviations: ARR = Aldosterone-to-Renin-Ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; AVS = Adrenal Venous Sampling.

an elevated ARR (33.4%) and in 102 patients (29.9%) the test indicated PA. Ninety-one of these 102 patients (89.2%) underwent CT and in 11 patients (10.8%) no CT was performed. These 11 patients underwent MRI and/or AVS. Sixty out of 91 patients (65.9%) also underwent AVS and in 57 (62.6%) patients the AVS indicated unilateral disease. When combining these results, 57 out of the 435 (13.1%) patients who had surgery within this cohort underwent the complete work-up as recommended by the 2008 Endocrine Society Guideline[8]. All other patients did not undergo all recommended diagnostic modalities or for instance had an ARR or confirmatory test not compatible with PA (Figure 3).

FIGURE 2 LARGE HETEROGENEITY IN THE USE OF CONFIRMATORY TESTING, MRI, CT AND AVS





Legend: This figure shows the use of different diagnostic modalities in the work-up of primary aldosteronism specified by continent and medical center. As presented, a large variability in work-up strategies was used in daily clinical practice and, in contrast to the guideline, confirmatory testing and AVS were not regularly performed.
Abbreviations: CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; AVS = Adrenal Venous Sampling.

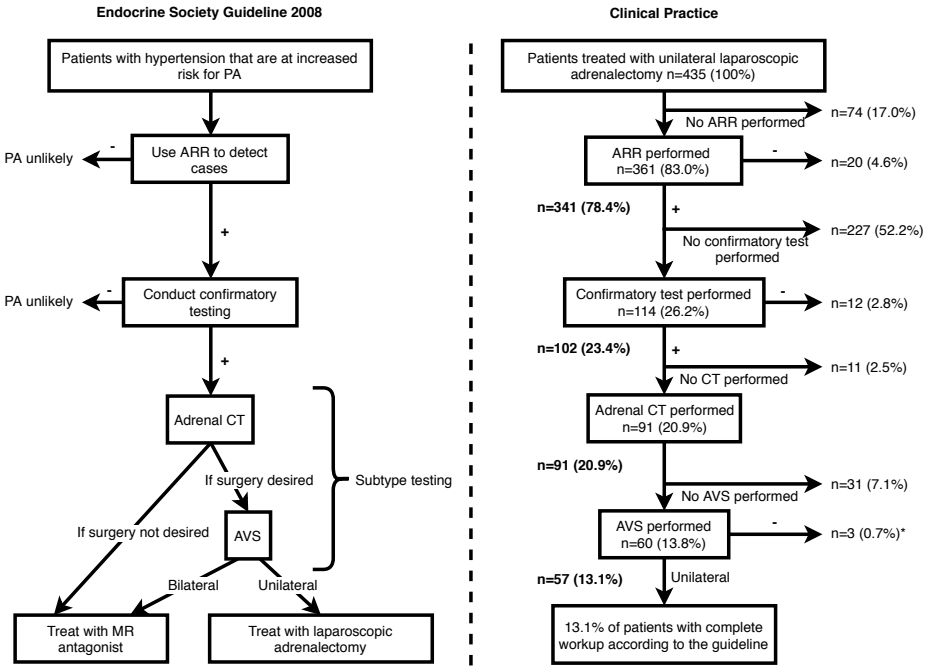
Evaluation of the 2016 Endocrine Society Guideline

Within the complete cohort, 177 patients (40.7%) preoperatively had elevated aldosterone, suppressed renin and spontaneous hypokalemia. Of the 114 patients in whom a confirmatory test was performed, sixty-five (57.0%) fulfilled these 3 criteria. In addition, 112 (49.3%) of the 227 patients in whom no confirmatory test was performed, did not meet these 3 criteria and therefore would indeed not require a confirmatory test according to the updated guidelines. When applying the recommendations of the most recent Endocrine Society Guideline, 51.9% of the patients with a positive ARR most likely did not have to undergo a confirmatory test. Among the 242 patients in whom a preoperative CT was performed, only 30 (12.4%) patients were younger than 35 years of age and only 14 (5.8%) patients also had an elevated aldosterone, spontaneous hypokalemia and a unilateral nodule on CT. According to the 2016 guideline these 14 (5.8%) patients did not have to undergo AVS[9].

Variables associated with performing AVS

Univariable analysis showed that AVS was more frequently performed in case of higher age, male gender, longer duration of hypertension, presence of hypokalemia, CT indicating bilateral disease or normal adrenal anatomy and a smaller tumor on CT (Table 3). After multivariable regression analysis, bilateral disease or normal adrenal anatomy on CT (OR 16.19; CI 3.50 – 74.99)($p<0.001$), smaller tumor size on CT (mm)(OR 0.06; CI 0.04 – 0.08)($p<0.001$) and hypokalemia (OR 2.00; CI 1.19 – 3.32)($p=0.008$) remained independently associated with performing AVS.

FIGURE 3 WORK-UP IN CURRENT CLINICAL PRACTICE IN CONTRAST TO THE ENDOCRINE SOCIETY GUIDELINE 2008



* 2 patients had failure of AVS procedure and in 1 patient AVS showed no lateralization.
Legend: This figure describes the work-up to surgery for primary aldosteronism in daily clinical practice as it was performed within this study cohort. The performed work-up was compared to the 2008 Endocrine Society Guideline as this was accurate during the inclusion period of the study. The figure shows low guideline adherence since 13.1% underwent the complete work-up according to the guideline. Patients were excluded when: (1) they did not undergo one of the recommended diagnostic test, (2) results of the aldosterone-to-renin ratio and confirmatory test did not correlate with primary aldosteronism, (3) results of adrenal venous sampling did not indicate unilateral aldosterone hypersecretion (all indicated by the horizontal arrows to the right).
Abbreviations: PA = Primary Aldosteronism; ARR = Aldosterone-to-Renin-Ratio; CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; AVS = Adrenal Venous Sampling.

DISCUSSION

This study evaluated the work-up to adrenalectomy for PA within current daily practice in an international retrospective cohort of surgical patients. Results displayed a large variability in work-up strategies within and between the participating centers worldwide. During the inclusion period of this study, the 2008 Endocrine Society Guideline was applicable[8]. Only 57 (13.1%) of the 435 operated patients underwent a complete work-up as was recommended by this guideline. Also, in contrast to the guideline, confirmatory testing and AVS were performed in only one third and two third of the operated patients, respectively. Therefore, this study illustrates that clinicians most likely chose a particular work-up strategy, such as the selective use of AVS, based on their preferences or guided by case specifics.

TABLE 3 VARIABLES ASSOCIATED WITH PERFORMING AVS FOR SUBTYPE TESTING

	Univariable analysis					Multivariable regression analysis with backward selection**	
	% missing	**CT + AVS (n=242)**	**CT only (n=136)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age (years)	0.0%	51.6 (11.0)	48.9 (11.1)	1.02 (1.00 – 1.04)	**0.026**	-	NS
Gender	0.0%						
Male		153 (71.8%)	60 (28.2%)	2.18 (1.42 – 3.34)	**<0.001**	-	NS
Female		89 (53.9%)	76 (46.1%)	1 (ref)			
Body mass index (kg/m²)	7.7%	30.0 (6.2)	29.0 (6.2)	1.03 (0.99 – 1.06)	0.153	-	
Duration of hypertension (years)*	14.8%	10 (0 – 40)	7 (0 – 38)	1.04 (1.01 – 1.08)	**0.016**	-	
Systolic blood pressure (mmHg)	0.0%	150 ± 19	149 (18)	1.00 (0.99 – 1.01)	0.635	NA	NA
Diastolic blood pressure (mmHg)	0.0%	90 ± 12	88 (11)	1.02 (1.00 – 1.04)	**0.067**	-	NS
Number of antihypertensives*	0.0%	3 (0 – 8)	3 (0 – 7)	1.03 (0.88 – 1.21)	0.846	NA	NA
Defined daily dose*	6.6%	3.7 (0.0 – 22.3)	3.2 (0.0 – 25.3)	1.03 (0.97 – 1.10)	0.332	NA	NA
ARR indicating PA	16.9%						
Yes		187 (63.6%)	107 (36.4%)	1.75 (0.71 – 4.33)	**0.223**	-	NS
No		10 (50.0%)	10 (50.0%)	1 (ref)			
Elevated Aldosterone	6.9%						
Yes		129 (66.2%)	66 (33.8%)	1.24 (0.80 – 1.92)	0.331	NA	NA
No		96 (61.1%)	61 (38.9%)	1 (ref)			
Suppressed Renin	8.5%						
Yes		137 (64.6%)	75 (35.4%)	1.41 (0.88 – 2.26)	**0.156**	-	NS
No		61 (56.5%)	47 (43.5%)	1 (ref)			
Hypokalemia	1.3%						
Yes		188 (67.6%)	90 (32.4%)	1.88 (1.17 – 3.02)	**0.009**	2.00 (1.19 – 3.32)	**0.008**
No		50 (52.6%)	45 (47.4%)	1 (ref)		1 (ref)	
CT outcome	1.1%						
Unilateral nodule		192 (59.1%)	133 (40.9%)	1 (ref)	**<0.001**	1 (ref)	
No unilateral nodule		47 (96.1%)	2 (3.9%)	16.28 (3.89 – 68.18)		16.19 (3.50 – 74.99)	**<0.001**
Bilateral nodule		26 (92.9%)	2 (7.1%)				
Normal anatomy		21 (100%)	0 (0%)				
CT tumor size (mm)*	6.8%	14 (0 – 29)	16 (6 – 95)	0.05 (0.04 – 0.07)	**<0.001**	0.06 (0.04 – 0.08)	**<0.001**

* Values not normally distributed given as medians (range)

** Variables with a p-value <0.25 after univariable analysis were used for multivariable regression analysis with backward selection.

Abbreviations: ARR = Aldosterone-to-Renin-Ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; AVS = Adrenal Venous Sampling; OR = odds ratio; CI = confidence interval; ref = reference variable; NS = Not Significant; NA = Not Applicable.

The Endocrine Society published a clinical guideline for PA in 2008 with the aim of improving the screening, work-up, treatment and follow-up worldwide[8]. Within this guideline, screening in hypertensive patients for PA is encouraged because the risk associated with missing a PA diagnosis surpasses the cons of exposing patients to additional diagnostic testing. Currently, the ARR is the recommended and most reliable test for screening for PA[8,9,18,19]. Confirmatory testing was recommended for all patients with a positive ARR to exclude false positive ARR results. However, this study shows the large variability in diagnostic work-up worldwide in which a confirmatory test was performed in only 32.9% of patients. The relatively low proportion of patients who underwent a confirmatory test and the large variability between the centers could be due to the fact that all confirmatory tests have some limitations and no universally accepted "gold standard'' confirmatory test for PA is identified in current literature[20-26]. Additionally, confirmatory tests are relatively expensive and frequently difficult to perform in outpatient settings[8,9]. This may have contributed to the changes in the 2016 guideline. Our data show that a relatively large proportion of patients (40.7%) fulfills the triad of marked aldosterone, suppressed renin and hypokalemia. Omitting confirmatory testing in these patients would have been in agreement with the revised guideline of 2016. Therefore, this change in the guideline could induce a substantial reduction in confirmatory testing. Nevertheless it should be noted that this revised recommendation is based on a relatively low level of evidence and therefore not performing a confirmatory test is not without risks. Especially because a patient with primary hypertension could be incorrectly diagnosed with PA and potentially undergo surgery based on false positive ARR results.

With respect to the diagnostic work up of PA there seems to be no consensus between experts on the use of AVS, as evidenced by the 34.7% of patients in this study who did not undergo AVS. Proponents argue that AVS should be considered as the "gold standard'' for subtype testing, because multiple studies have shown its superiority over CT in determining disease lateralization. In these studies, results of CT were compared to AVS as reference standard[11,27,28]. Opponents of AVS argue on the practical difficulties such as higher costs and the need of an interventional radiologist. This limits the wide availability of AVS, because some centers do not have the financial resources or expertise to perform AVS[10,29,30]. In addition, AVS is an invasive procedure and also has failure and complication rates. Furthermore, they argue that no significant differences in outcomes, such as antihypertensive medications or quality of life, were observed between CT and AVS within a randomized trial[31].

In this study all participating medical centers used AVS in at least some patients. This suggests that AVS was available for all medical centers during some period of the inclusion period. Hence, we speculate that clinicians most likely chose to perform or not perform AVS based on their preferences or guided by case specifics. AVS was more frequently performed on patients with higher age, male gender, longer duration of hypertension and preoperative hypokalemia. Potentially, these represent the patients with more severe hypertension and/or hyperaldosteronism since some of these factors are also known as risk factors for less favorable clinical outcomes after adrenalectomy[12,32,33]. Furthermore, AVS was more frequently done in

case of smaller tumor size, bilateral disease or normal adrenal anatomy on CT. Recently Williams *et al.* also showed that AVS was more frequently performed in case of male gender and smaller tumor size on CT in univariable analysis[34]. Furthermore, they indicated that AVS was used more often in case of lower blood pressure, higher ARR and lower estimated glomerular filtration rate[34].

Results of multivariable analysis within our cohort showed that hypokalemia and CT findings remained independently associated with performing AVS. Regarding the CT findings, the analysis showed that the presence of bilateral disease or normal adrenal anatomy on CT proved to be the most important trigger for clinicians to use AVS in daily practice (OR 16.19; CI 3.50 – 74.99)(p<0.001). Likewise, 96.1% of patients with bilateral disease or normal adrenal anatomy on CT also underwent AVS. In contrast, patients with a clear unilateral nodule on CT and especially patients with larger tumors were less likely to undergo AVS. This further supports that CT findings most likely have the highest influence on the choice to perform or not perform AVS in daily clinical practice. The 2016 guideline allows the omission of AVS in case of a clear unilateral cortical adenoma on CT when this is combined with hypokalemia, age < 35 years and marked aldosterone excess. Within this study only 6% of patients met these conditions. Consequently, this new recommendation only has marginal influence on daily practice.

This study has some limitations. Similar to the majority of studies on PA, the retrospective design is a weakness. As a result, this study is more prone to missing data compared to prospective studies. Potentially, this could have led to lower rates of performed preoperative measurements of the ARR and confirmatory testing, as we chose to classify these modalities as not performed when results were not known within the local patient files or referral letters. On the other hand, the retrospective design most likely is appropriate to evaluate different types of work-up strategies in clinical practice, as it reduces the influence of study protocols on decisions made by clinicians and therefore reflects daily practice. Another limitation of this study is the derivation of this cohort for a different study aim[15]. During this derivation, 15% of the surgical patients were excluded due to missing data regarding blood pressure related preoperative of postoperative variables. Because the present study has a different study aim, these patients could have been included within this study[15].

The blood pressure related outcomes within this cohort were published earlier and therefore not reported within this manuscript[15,16]. As presented within these and other recently published studies, complete cure of hypertension after the operation is far from a certainty[12,15,16]. Potentially this is due to the large variability in work-up strategies which stresses the importance of evaluating how we currently perform the work-up to surgery for PA. Nevertheless, our study cohort is not suitable for properly investigating the potential influence of the presented uniformity in work-up strategies on the outcomes after surgery. This is due to the retrospective design which is prone to confounding by indication.

In conclusion, this study examined the work-up to surgery for PA within current worldwide daily clinical practice. Results demonstrate large variability in work-up strategies with relatively low guideline adherence. Most likely this is a reflection of the work-up related controversies between experts in the field of PA which are due to the lack of convincing evidence in current literature and low level of evidence for some guideline recommendations. If we want to further improve the benefits of surgery for PA in the future, studies should be performed to generate valid evidence and consensus on the required work-up before surgery.

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PART

2

BENEFITS OF SURGERY IN PRIMARY ALDOSTERONISM

CHAPTER

4

Clinical outcomes after unilateral adrenalectomy for primary aldosteronism

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ABSTRACT

Importance
Besides biochemical cure, clinical benefits after surgery for primary aldosteronism (PA) depend on the magnitude of decrease in blood pressure (BP) and usage of antihypertensive medications with subsequent decreased risk of cardiovascular/cerebrovascular morbidity and drug-induced side-effects.

Objective
To describe the decrease in BP and antihypertensive medications within an international cohort of recently operated patients.

Design
Retrospective-cohort study.

Setting
Multicenter study across 16 referral medical centers in Europe, the United States, Canada and Australia.

Participants
We analyzed patients who underwent unilateral adrenalectomy for PA between 2010 and 2016. Unilateral disease was confirmed using computed tomography, magnetic resonance imaging and/or adrenal venous sampling. Patients with missing/incomplete preoperative or follow-up data regarding BP or corresponding number of antihypertensive medications were excluded. In total, 435 (85%) patients were eligible from a cohort of 514 unilateral adrenalectomy patients based on inclusion and exclusion criteria.

Main outcome and measures
Clinical success was defined based on postoperative BP and number of antihypertensive medications. Cure was defined as normotension without antihypertensive medications. Clear improvement was defined as normotension with lower (or equal) use of antihypertensive medications. In case of preoperative normotensivity, a decrease of antihypertensive use was required. All other patients were stratified as no clear success because, mainly due to postoperative persistent hypertension benefits of surgery were less obvious. Clinical outcomes were assessed at follow-up closest to 6 months after surgery.

Results
Cure was achieved in 27%, clear improvement in 31% and no clear success in 42% of patients. In the subgroup classified as no clear success 91% had postoperative hypertension. However, within this subgroup, the mean systolic and diastolic BP still decreased significantly by 9±22 mmHg ($p<0.0001$) and 3±15 mmHg ($p=0.04$), respectively. Also the use of antihypertensive medications decreased by 50% ($p<0.0001$). Moreover, in 41% of patients within this subgroup the decrease in systolic BP was ≥ 10 mmHg.

Conclusion
In the majority of patients (58%), adrenalectomy leads to a postoperative normotensive state and reduction of antihypertensive medications. Furthermore, a significant proportion of patients with postoperative persistent hypertension also benefits from adrenalectomy given the observed clinically relevant and significant reduction of BP and antihypertensive medications.

INTRODUCTION

Primary aldosteronism (PA), is the most common form of secondary hypertension. The disease is characterized by inappropriate endogenous production of the mineralocorticoid aldosterone by one or both of the adrenal glands[1,2]. Prevalence is estimated at 5% in the general hypertensive population and even higher in populations with severe/resistant hypertension[3-5]. Due to aldosteronism itself and subsequent (resistant) hypertension, PA leads to long-term fibrosis and remodeling in critical organs resulting in increased risk of cardiovascular, cerebrovascular and renal morbidity and mortality[6-9]. Therefore, PA could be considered a serious health issue[9,10].

In the vast majority of cases, PA is accounted for by either an aldosterone-producing adenoma (APA), generally treated with adrenalectomy, or bilateral adrenal hyperplasia, treated with mineralocorticoid receptor antagonists[10]. Adequate treatment of PA leads to significant reduction of morbidity and mortality through cure or improvement of aldosteronism and hypertension[11,12]. Biochemical cure (i.e., normalization of plasma aldosterone levels) is achieved in almost all patients following adrenalectomy (96-100%)[13]. However, results on clinical cure (i.e., postoperative normotensive state without the use of antihypertensive medications) vary extensively across studies (22 – 84%)[13-15].

Recent systematic reviews and meta-analysis have indicated clinical cure on pooled data in 42%, 50% and 52% of patients[13-15]. These reviews include numerous studies presenting clinical outcomes after adrenalectomy published over the last decades[13-15]. However, the majority of included studies were single center with small study populations. In studies with larger study populations, the cohort was frequently spanning multiple decades with the potential introduction of bias because of improvement in diagnosis, work-up, and treatment of PA with updated guidelines as well as innovations in diagnostics modalities and surgical techniques over time. Moreover, also the worldwide increase of hypertension over the last decades could influence the hypertension related outcomes after surgery due to the increase in not PA related (i.e., background/essential) hypertension[16]. Furthermore, these studies were mainly focused on presenting proportions of patients with clinical cure or improvement and identifying possible prognostic factors instead of describing the decrease of blood pressure and antihypertensive medications, which is important for daily clinical practice[17,18].

Because clinical benefits of surgery mostly depend on the magnitude of blood pressure decrease rather than crossing the blood pressure threshold that currently defines hypertension, we hypothesized that precise presentation of decrease in blood pressure and use of antihypertensive medications after adrenalectomy leads to better understanding of the benefits of surgery in PA[19]. Therefore, we set out to investigate and precisely display the effect of adrenalectomy on blood pressure and the need for antihypertensive medications in a large and international cohort of patients who underwent adrenalectomy for PA between 2010 and 2016. In addition, we hypothesized that also patients in which the benefits of surgery are less obvious, for instance due to persistent hypertension after adrenalectomy, could benefit from surgery. Especially because every 10 mmHg reduction in systolic blood pressure results in significant reduction of cardiovascular morbidity and mortality[19]. Therefore we chose to precisely illustrate the effect of surgery within this specific subgroup as well.

METHODS

Patients

We performed an international retrospective cohort study across 16 referral/tertiary medical centers in the United States, Europe, Canada and Australia (Table 2). All patients who underwent unilateral adrenalectomy between 2010 and 2016 for APA, proven by Computerized Tomography (CT) and/or Magnetic Resonance Imaging (MRI) and/or Adrenal Venous Sampling (AVS) were included. Patients with missing/incomplete preoperative or follow-up data regarding systolic blood pressure (SBP), diastolic blood pressure (DBP) or corresponding number of antihypertensive medications (AHTN) were excluded. Institutional review board approval was obtained in all participating centers. Data collection was performed separately within each center with the use of a standardized data-entry-manual. Patient demographics, disease characteristics, laboratory data (e.g., measurements of aldosterone-to-renin ratio (ARR) and potentially confirmatory tests), results of CT/MRI/AVS, operative characteristics, pathology diagnosis and timing of follow-up were collected. To compare laboratory data between centers, measurements were classified as elevated or suppressed when values were above or below the local reference ranges.

Outcomes and definitions

The primary outcomes of this study were the preoperative to postoperative change in SBP and DBP (mmHg) with subsequent change in antihypertensive medications. If multiple preoperative or postoperative blood pressure measurements were performed (on the same antihypertensive medications) the mean SBP and DBP were calculated. In general, office blood pressure measurements were performed during outpatient visitation. If 24-hour ambulatory blood pressure measurements were available this was preferred. The number of different antihypertensive medications, names and dosage used at the time of blood pressure measurements were collected. When medications were discontinued due to diagnostics testing, such as the ARR or a confirmatory test, SBP and DBP with corresponding medications

before discontinuation were used. The number of AHTN was defined as the number of different antihypertensive medication categories used (e.g., calcium channel blockers, beta blockers, etc.). If data was sufficient also the defined daily dose (DDD), based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC)/DDD Index 2017 (see https://www.whocc.no/atc_ddd_index/), and the number of pills taken by the patient each day were calculated. Hypertension grade was based on blood pressure with medicationx[20,21]. Grade 0 was defined as SBP < 140 and DBP < 90 mmHg, Grade 1 as SBP 140 – 159 and/or DBP 90 – 99 mmHg, Grade 2 as SBP 160 – 179 and/or DBP 100 – 109 mmHg, and Grade 3 as SBP ≥ 180 or DBP ≥ 110 mmHg. Clinical success was stratified as cure, clear improvement or no clear success based on postoperative SBP/DBP and number of AHTN. Cure was defined as a postoperative normotensive patient (i.e., SBP < 140 and DBP < 90 mmHg) without the need of antihypertensive medicationx[20,21]. Clear improvement was defined as a postoperative normotensive patients on lower (or equal) number of AHTN. In case of preoperative normotensive patient, a decrease in number of AHTN was required. All other patients were stratified as no clear success because the possible benefits of surgery within this subgroup were less obvious, mainly due to persistent hypertension after surgery. We also stratified based on magnitude of systolic blood pressure decrease (i.e., <10 mmHg, 10 – 19 mmHg, 20 – 29 mmHg, 30 – 39 mmHg, 40 – 49 mmHg, ≥50 mmHg). For this stratification all patients with an increase in number of AHTN were excluded to minimalize the possible effect of increased medication on decrease in SBP. The goal was to assess primary outcomes at follow-up closest to 6 months after adrenalectomy (range 3 – 9 months). Mainly due to geographic distances multiple medical centers were not able to complete this 6 months of follow-up (range 3 – 6 months). 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

Normally and not normally distributed continuous data are shown as mean (± standard deviation) and median (range). The McNemar's test was used for paired nominal data, the paired sample T-test for paired normally distributed continuous data and the Wilcoxon signed ranked test for paired not normally distributed continuous data. To compare continuous variables between groups the Mann-Whitney *U* Test (2 groups) or Kruskal-Wallis Test (>2 groups) was used for not normally distributed data and One-Way ANOVA for normally distributed data. The Chi-Square test and Fisher's exact test were used to analyze group differences for categorical variables. Statistical analysis was performed using SPSS version 23.0 (Chicago, Illinois, USA).

RESULTS

In total 514 patients underwent unilateral adrenalectomy for PA between 2010 and 2016. Based on inclusion and exclusion criteria 435 (85%) patients were eligible for further analysis. The primary reason for exclusion was inadequate preoperative and/or postoperative data

regarding blood pressure and number of AHTN. The cohort consisted of 186 (43%) females and the mean age was 50.7 ± 11.4 years. Hypokalemia was present in 74% of patients and the vast majority of patients (95%) had an ARR indicating PA. CT, AVS and MRI were performed in 88%, 64% and 17% of patients, respectively. Further baseline characteristics are shown in Table 1. Distribution of operated patients and period of follow-up per medical center is shown in Table 2.

Overall effect of surgery on blood pressure and antihypertensive medications (Table 3)
In the entire cohort the preoperative mean SBP and DBP were 150 ± 20 and 90 ± 13 mmHg. Grade 1 hypertension was most frequent (41%). The preoperative median number of AHTN, DDD and number of pills taken each day were 3 (0 – 8), 3.7 (0.0 – 25.3) and 3 (0 – 10), respectively. After surgery the mean SBP and DBP were decreased to 133 ± 16 mmHg and 83 ± 10 mmHg resulting in a reduction of 17 ± 21 mmHg (10.3% ± 13.2%) and 7 ± 14 mmHg (7.0% ± 14.5%)(all p<0.001). Also, the number of AHTN, DDD and number of pills were reduced by a median of 60%, 73%, and 67%, respectively (all p<0.001). Two hundred and sixty-nine patients (61.8%) had grade 0 and therefore were normotensive after surgery (including patients with and without antihypertensive medications).

Clinical success: cure, clear improvement and no clear success (Table 3)
Cure was achieved in 118 (27%) patients, clear improvement in 135 (31%) patients and no clear success in 182 (42%) of patients. Within the group stratified as cure the mean SBP and DBP decreased significantly, 21± 18 mmHg (13.4% ± 11.2%) and 9 ± 11 mmHg (9.6% ± 12.9%) (both p<0.001). As per definition, within this subgroup all antihypertensive medications were stopped. Within the group stratified as improvement the mean SBP and DBP decreased significantly, 25 ± 18 mmHg (15.6% ± 10.1%) and 12 ± 12 mmHg (11.9% ± 12.6%)(both p<0.001). The median number of AHTN, DDD and number of pills reduced by 50%, 48% and 50%, respectively (all p<0.001). Also in the group stratified as no clear success the mean SBP and DBP were significantly decreased by 9 ± 22 mmHg (4.3% ± 14.0%)(p<0.0001) and 3 ± 15 mmhg (1.5% ± 15.1%)(p=0.04). The median number of AHTN, DDD and number of pills decreased significantly by 50%, 53% and 50%, respectively (all p<0.001). Pair-wise comparison between the three groups showed similar magnitude of decrease in SBP and DBP between cure and clear improvement. Furthermore, it is interesting to note, that the decrease in DDD was comparable between the 3 groups (p=0.52). This was due to the significant lower preoperative DDD within patients with cure compared to clear improvement (p<0.001) and no clear success (p<0.001). Geographic stratification of the rates of clinical success and other blood pressure related outcomes for the United States, Europa, Canada and Australia is presented in Supplement 1.

TABLE 1 BASELINE CHARACTERISTICS OF 435 PATIENTS

Variable	Number (%) or mean ± SD
Age at surgery (years)	50.7 ± 11.4
Female	186 (43%)
Duration of HTN (years) (n=366)*	9 (0 – 42)
Body mass index(n=402)	29.7 ± 6.0
No. AHTN*	3 (0 – 8)
Hypokalemia (n=429)	317 (74%)
History of cardiovascular events (n=431)	62 (14%)
Diabetes (n=432)	57 (13%)
Current smoker (n=417)	48 (12%)
Hypercholesterolemia (n=430)	114 (27%)
Family history of HT (n=338)	173 (40%)
Preoperative mean SBP (mmHg)	150 ± 20
Preoperative mean DBP (mmHg)	90 ± 13
JNC/ESH hypertension grade based on blood pressure with medication	
Grade 0	111 (26%)
Grade 1	180 (41%)
Grade 2	105 (24%)
Grade 3	39 (9%)
Elevated aldosterone level (n=408)	225 (55%)
Suppressed renin level/activity (n=370)	245 (66%)
ARR indicating PA (n=361)	341 (95%)
Elevated creatinine level (n=392)	71 (18%)
CT performed (n=432)	378 (88%)
AVS performed (n=434)	278 (64%)
MRI performed (n=434)	72 (17%)
Confirmatory test performed	143 (33%)
Oral salt loading	18 (4%)
Saline infusion test	118 (27%)
Fludrocortisone suppression test	3 (<1%)
Captopril challenge	1 (<1%)
Fludrocortisone dexamethasone suppression test	1 (<1%)
Post-low dose dexamethasone suppression – saline infusion test	1 (<1%)
Surgical procedure	
EPRA	171 (39%)
ELRA	65 (15%)
LTA	198 (46%)
Open	1 (<1%)
Robot assisted	17 (4%)
Conversion	2 (<1%)
Tumor laterality	
Left	260 (60%)
Right	175 (40%)
Histology	
Adenoma	362 (83%)
Hyperplasia	58 (13%)
Adenoma/hyperplasia	13 (3%)
Missing	1 (<1%)
Hospital stay (days)*	1 (0 – 70)

TABLE 1 (CONTINUED) BASELINE CHARACTERISTICS OF 435 PATIENTS

Variable	Number (%) or mean ± SD
Follow up after surgery	
< 1 month	101 (23%)
1 – < 3 months	39 (9%)
3 – 9 months	278 (64%)
> 9 – 12 months	4 (<1%)
12 – 18 months	13 (3%)

* Values not normally distributed given as medians (range)
Abbreviations: HTN = hypertension; No. = Number of; AHTN = Antihypertensive medications; JNC = Joint National Commission; ESH = European Society of Hypertension; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ARR = Aldosterone-to-Renin-Ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; AVS = Adrenal Venous Sampling; MRI = Magnetic Resonance Imaging; EPRA = Endoscopic Posterior Retroperitoneal Adrenalectomy; ELRA = Endoscopic Lateral Retroperitoneal Adrenalectomy; LTA = Laparoscopic Transabdominal Adrenalectomy.

TABLE 2 DISTRIBUTION OF INCLUDED PATIENT PER CENTER AND PERIOD OF FOLLOW-UP

Medical center	Operated* 2010 – 2016	Eligible* 2010 – 2016	Period of follow-up after surgery (months)				
			< 1	1 – < 3	3 – 9	> 9 – 12	> 12 – 18
University of California San Francisco Medical Center	82	69 (84%)	49 (71%)	5 (7%)	15 (22%)	0 (0%)	0 (0%)
Northwestern Memorial Hospital	51	43 (84%)	19 (44%)	4 (9%)	19 (44%)	1 (2%)	0 (0%)
Royal North Shore Hospital	51	39 (76%)	0 (0%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)
Weill Cornell Medical Center	47	40 (85%)	2 (5%)	0 (0%)	37 (93%)	0 (0%)	1 (3%)
Columbia University Medical Center	46	40 (87%)	3 (8%)	1 (2%)	36 (90%)	0 (0%)	0 (0%)
University Health Network Toronto	44	32 (73%)	2 (6%)	8 (25%)	19 (60%)	0 (0%)	3 (9%)
University Medical Center Groningen	41	36 (88%)	0 (0%)	2 (6%)	28 (78%)	2 (6%)	4 (11%)
University Medical Center Utrecht	40	37 (93%)	2 (5%)	5 (14%)	28 (76%)	1 (3%)	1 (3%)
University of Chicago Medicine	26	25 (96%)	15 (60%)	0 (0%)	10 (40%)	0 (0%)	0 (0%)
M.D. Anderson Cancer Center	19	19 (100%)	6 (32%)	6 (32%)	6 (32%)	0 (0%)	1 (5%)
Instituto de Semeiotica Chirurgica Roma	16	9 (56%)	0 (0%)	0 (%)	9 (0%)	0 (0%)	0 (0%)
Academic Medical Center Amsterdam	15	11 (73%)	0 (0%)	0 (0%)	11 (100%)	0 (0%)	0 (0%)
Bosten Medical Center	12	12 (100%)	1 (8%)	3 (25%)	8 (67%)	0 (0%)	0 (0%)
Montreal General Hospital – McGill University Health Center	10	10 (100%)	1 (10%)	1 (10%)	8 (80%)	0 (0%)	0 (0%)
VU University Medical Center	8	8 (100%)	0 (0%)	4 (50%)	1 (13%)	0 (0%)	3 (40%)
University Medical Center Maastricht	6	5 (83%)	1 (20%)	0 (0%)	4 (80%)	0 (0%)	0 (0%)
Total	**514**	**435 (85%)**	**101 (23%)**	**39 (9%)**	**278 (64%)**	**4 (1%)**	**13 (3%)**

*The median number of operated and eligible patients percenters was 33 (6 – 82) and 28.5 (5 – 69), respectively.

TABLE 3 CLINICAL SUCCESS: CURE, CLEAR IMPROVEMENT AND NO CLEAR SUCCESS

Variable	Total cohort (n=435)	Clinical success			Comparison between groups (p-value)			
		Cure (n=118) (27%)	Clear improvement (n=135) (31%)	No clear success (n=182) (42%)	Overall	Pairwise		
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*		CURE vs. CIMP	CURE vs. NCS	CIMP vs. NCS.
Preoperative								
Mean SBP (mmHg)	150 ± 20	143 ± 17	150 ± 17	155 ± 22	**<0.001**	**0.007**	**<0.001**	0.07
Mean DBP (mmHg)	90 ± 13	88 ± 11	90 ± 12	91 ± 15	0.07	0.56	0.07	1.00
Preoperative hypertension grade					**<0.001**	**<0.001**	**<0.001**	**0.032**
Grade 0	111 (25.5%)	49 (41.5%)	27 (20.0%)	35 (19.2%)				
Grade 1	180 (41.4%)	41 (34.7%)	70 (51.9%)	69 (37.9%)				
Grade 2	105 (24.1%)	24 (20.3%)	27 (20.0%)	54 (29.7%)				
Grade 3	39 (9.0%)	4 (3.4%)	11 (8.1%)	24 (13.2%)				
No. AHTN (/day)*	3 (0 – 8)	2 (0 – 6)	3 (1 – 8)	3 (0 – 7)	**<0.001**	**<0.001**	**<0.001**	0.27
DDD (n=405)*	3.7 (0.0 – 25.3)	2.2 (0.0 – 15.7)	4.1 (0.5 – 25.3)	4.3 (0.0 – 22.3)	**<0.001**	**<0.001**	**<0.001**	0.86
No. pills (/day) (n=407)*	3 (0 – 10)	2 (0 – 7)	4 (1 – 10)	4 (0 – 9)	**<0.001**	**<0.001**	**<0.001**	0.22
Postoperative								
Mean SBP (mmHg)	133 ± 16	122 ± 9	126 ± 9	147 ± 15	**<0.001**	0.12	**<0.001**	**<0.001**
Mean DBP (mmHg)	83 ± 10	78 ± 7	78 ± 7	89 ± 11	**<0.001**	1.00	**<0.001**	**<0.001**
Postoperative hypertension grade					**<0.001**	1.00	**<0.001**	**<0.001**
Grade 0	269 (61.8%)	118 (100.0%)	135 (100.0%)	16 (8.8%)				
Grade 1	117 (26.9%)	0 (0.0%)	0 (0.0%)	117 (64.3%)				
Grade 2	41 (9.4%)	0 (0.0%)	0 (0.0%)	41 (22.5%)				
Grade 3	8 (1.8%)	0 (0.0%)	0 (0.0%)	8 (4.4%)				

TABLE 3 (CONTINUED) CLINICAL SUCCESS: CURE, CLEAR IMPROVEMENT AND NO CLEAR SUCCESS

Variable	Total cohort (n=435)	Clinical success			Comparison between groups (p-value)			
		Cure (n=118) (27%)	Clear improvement (n=135) (31%)	No clear success (n=182) (42%)	Overall	Pairwise		
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*		CURE vs. CIMP	CURE vs. NCS	CIMP vs. NCS.
No. AHTN (/day)*	1(0 – 6)	0 (0 – 0)	2 (1– 5)	2 (0 – 6)	**<0.001**	**<0.001**	**<0.001**	0.30
DDD (n=402)*	1.0 (0.0 – 11.7)	0.0 (0.0 – 0.0)	2.0 (0.1 – 11.7)	2.0 (0.0 – 9.8)	**<0.001**	**<0.001**	**<0.001**	0.25
No. pills (/day) (n=407)*	1 (0 – 9)	0 (0 – 0)	2 (0 – 8)	2 (0 – 9)	**<0.001**	**<0.001**	**<0.001**	0.38
Preoperative-postoperative change†								
SBP (mmHg)	17 ± 21	21 ± 18	25 ± 18	9 ± 22	**<0.001**	0.28	**<0.001**	**<0.001**
DBP (mmHg)	7 ± 14	9 ± 11	12 ± 12	3 ± 15	**<0.001**	0.49	**<0.001**	**<0.001**
SBP (%)	10.3% ±13.2%	13.4% ± 11.2%	15.6% ± 10.1%	4.3% ± 14.0%	**<0.001**	0.45	**<0.001**	**<0.001**
DBP (%)	7.0% ± 14.5%	9.6% ± 12.9%	11.9% ± 12.6%	1.5% ± 15.1%	**<0.001**	0.55	**<0.001**	**<0.001**
No. AHTN (/day)*	2 (-3– 6)	2 (0 – 6)	1 (0 – 5)	1 (-3 – 5)	**<0.001**	**<0.001**	**<0.001**	0.58
No. AHTN (/day) (%)*	60% (-100% –100%)	100% (0% –100%)	50% (0% – 80%)	50 % (-100% – 100%)	**<0.001**	**<0.001**	**<0.001**	0.68
DDD (n=382)*	2.0 (-4.7 – 24.3)	2.2 (0.0 – 15.7)	1.9 (-4.7 – 24.3)	2.0 (-4.3 – 20.7)	0.52	0.28	0.36	0.81
DDD (%)(n=382)*	73% (-400% – 100%)	100% (0% – 100%)	48% (-275 % – 99%)	53.1% (-400% – 100%)	**<0.001**	**<0.001**	**<0.001**	0.05
No. pills (/day) (n=388)*	2 (-3 – 8)	2 (0 – 7)	2 (-2 – 8)	2 (-3 – 6)	**0.02**	0.11	**0.005**	0.21
No. pills (/day) (%) (n=388)*	67% (-200% – 100%)	100% (0% – 100%)	50% (-200% – 100%)	50% (-100% –100%)	**<0.001**	**<0.001**	**<0.001**	0.85

* Values not normally distributed given as medians (range)

† Within all outcome variables (also within cure, clear improvement and no clear success) the preoperative-postoperative delta's showed significant decrease ($p<0.05$).

Abbreviations: CIMP = Clear improvement; NCS = No clear success; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; No. = Number of; AHTN = Antihypertensive medications; JNC = Joint National Commission; ESH = European Society of Hypertension; DDD= Defined Daily Dose.

Sub-analysis of those patients classified as having no clear success, in which the benefits of surgery were less obvious, is shown in Table 4. This group consisted of 166 (91%) patients with postoperative hypertension and 16 (9%) patients who were normotensive after surgery however showed increase in number of AHTN or no decrease in number of AHTN in cases with preoperative normotension. Within the group with postoperative hypertension, 26 (16%) patients were normotensive before surgery and showed an increase of SBP and DBP by 17 ± 14 mmHg and 9 ± 9 mmHg (both $p<0.001$) after surgery. On the other hand, the number of AHTN, DDD and number of pills decreased significantly by 67%, 83% and 67%, respectively (all $p<0.001$). The other 140 (84%) patients were hypertensive before and after surgery however showed a significant reduction of SBP and DBP by 13 ± 21 mmHg ($p<0.001$) and 4 ± 15 mmHg ($p=0.001$). Also the number of AHTN, DDD and number of pills decreased significantly by 50%, 58% and 50%, respectively (all $p<0.001$). Within the 16 patients who were normotensive after surgery, 9 (56%) patients were normotensive before and after surgery. They showed no significant change is blood pressure or antihypertensive medications. The other 7 (44%) patients were hypertensive before operation and although SBP and DBP were decreased significant by 29 ± 15 mmHg ($p=0.02$) and 18 ± 14 mmHg ($p=0.03$) in these patients, they were classified as no success due to an increase in number of AHTN.

Clinical success: magnitude of preoperative-postoperative change in SBP (Table 5)
Fourteen out of 435 (3%) patients showed an increase in number of AHTN after surgery and therefore possible decrease in SBP could be due to medication. The remaining 421 (97%) patients showed decreased or equal number of AHTN after surgery. In the total population, 76 (18%) patients had increase in SBP. However, 12 (16%) of these patients still were normotensive without antihypertensive medication (cure) and 8 (10%) patients were normotensive with the decreased or equal number of AHTN (clear improvement). Seventy-one (16%) patients showed a decrease in SBP between 0 – 9 mmHg, 87 (20%) patients a decrease between 10 – 19 mmHg, 84 (19%) patients a decrease between 20 – 29 mmHg, 51 (12%) patients a decrease between 30 – 39 mmHg, 24 (6%) patients a decrease between 40 – 49 mmHg and 28 (6%) patients a decrease ≥ 50 mmHg. Within the subgroups stratified as cure and clear improvement a decrease of SBP between 20 – 30 mmHg and 10 – 19 mmHg were most frequent, 25% and 27% respectively. Within the subgroup stratified as no clear success an increase in SBP was most frequent (31%). On the other hand, 41% of patients within the no clear success subgroup still had a decrease in SBP ≥ 10 mmHg.

DISCUSSION

Normalization of hyperaldosteronism after adrenalectomy for PA, which is shown in most cases, does not always lead to normalization of the blood pressure. Therefore, the assessment of clinical success (i.e., decrease in blood pressure and/or antihypertensive medications) after adrenalectomy is an important indicator for surgical effect. This study describes the effect of adrenalectomy on blood pressure and use of antihypertensive medications within a global

TABLE 4 SUBGROUP ANALYSIS OF PATIENTS STRATIFIED AS NO SUCCESS

Variable	No clear succes (n=182)	Postoperative hypertension (n=166)(91 %)	Postoperative normotension (n=16)(9%)	Comparison between groups (p-value)
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	
Preoperative				
Mean SBP (mmHg)	155 ± 22	156 ± 21	139 ± 16	**0.001**
Mean DBP (mmHg)	91 ± 15	92 ± 14	82 ± 12	**0.006**
Preoperative hypertension grade				**0.001**
Grade 0	35 (19.2%)	26 (15.7%)	9 (56.3%)	
Grade 1	69 (37.9%)	65 (39.2%)	4 (25.0%)	
Grade 2	54 (29.7%)	51 (30.7%)	3 (18.8%)	
Grade 3	24 (13.2%)	24 (14.5%)	0 (0.0%)	
No. of AHTN (/day)*	3 (0 – 7)	3 (0 – 7)	2 (0 – 6)	0.06
DDD (n=173)*	4.3 (0.0 – 22.3)	4.3 (0.0 – 22.3)	4.0 (0.0 – 12.0)	0.43
No. pills (/day) (n=173)*	4 (0 – 9)	4 (0 – 9)	2 (0 – 9)	**0.02**
Postoperative				
Mean SBP (mmHg)	147 ± 15	149 ± 13	122 ± 13	**<0.001**
Mean DBP (mmHg)	89 ± 11	90 ± 10	74 ± 9	**<0.001**
Postoperative hypertension grade				**<0.001**
Grade 0	16 (8.8%)	0 (0.0%)	16 (100.0%)	
Grade 1	117 (64.3%)	117 (70.5%)	0 (0.0%)	
Grade 2	41 (22.5%)	41 (24.7%)	0 (0.0%)	
Grade 3	8 (4.4%)	8 (4.8%)	0 (0.0%)	
No. AHTN (/day)*	2 (0 – 6)	1 (0 – 6)	3.5 (1 – 6)	**<0.001**
DDD (n=166)*	2.0 (0.0 – 9.8)	1.7 (0.0 – 7.5)	3.4 (1.0 – 9.8)	**0.01**
No. pills (/day) (n=168) *	2 (0 – 9)	1 (0 – 8)	4 (0 – 9)	**0.001**
Preoperative-postoperative delta				
SBP (mmHg)	9 ± 22†	8 ± 23†	16 ± 17†	0.16
DBP (mmHg)	3 ± 15†	2 ± 15	8 ± 15†	0.12
SBP (%)	4.3% ± 14.0%†	3.6% ± 14.1%†	10.9% ± 11.6%†	**0.05**
DBP (%)	1.5% ± 15.1%†	0.9% ± 14.7%	8.3% ± 17.4%†	0.06
No. AHTN (/day)*	1 (-3 – 5)†	2 (-2 – 5)†	0 (-3 – 0)	**<0.001**
No. AHTN (/day) (%)*	50 % (-100% – 100%)†	50% (-100 – 100%)†	0% (-100 – 0%)	**<0.001**
DDD(n=160)*	2.0 (-4.3 – 20.7)†	2.0 (-4.3 – 20.7)†	0.0 (-4.0 – 9.5)	**0.006**
DDD (%) (n=160)*	53% (-400% – 100%)†	60% (-256% – 100%)†	0% (-400% – 79%)	**0.001**
No. pills (/day) (n=163)*	2 (-3 – 6)†	2 (-3 – 6)†	0 (-3 – 1)	**<0.001**
No. pills (/day) (%)(n=163)*	50% (-100% – 100%)†	50% (-100% – 100%)†	0% (-100% – 50%)	**<0.001**

* Values not normally distributed given as medians (range)

† Significant (p<0.05) preoperative-postoperative delta.

Abbreviations: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; No. = Number of; AHTN = Antihypertensive medications; JNC = Joint National Commission; ESH = European Society of Hypertension; DDD= Defined Daily Dose.

TABLE 5 EFFECT OF SURGERY STRATIFIED BASED ON MAGNITUDE OF CHANGE IN SYSTOLIC BLOOD PRESSURE

Variable	Total cohort	Clinical success		
		Cure	Clear improvement	No clear success
	(n=435)	(n=118)	(n=135)	(n=182)
Decrease in SBP (mmHg)				
Increase	76 (18%)	12 (10%)†	8 (6%)†	56 (31%)
0 – 9	71 (16%)	21 (18%)	13 (10%)	37 (20%)
10 – 19	87 (20%)	22 (19%)	36 (27%)	29 (16%)
20 – 29	84 (19%)	29 (25%)	35 (26%)	20 (11%)
30 – 39	51 (12%)	19 (16%)	19 (14%)	13 (7%)
40 – 49	24 (6%)	7 (6%)	12 (9%)	5 (3%)
≥ 50	28 (6%)	8 (7%)	12 (9%)	8 (4%)
Increase in No. AHTN*	14 (3%)	0 (0%)	0 (0%)	14 (7%)

* Due to increase in number of AHTN decrease of SBP could be due to medication instead of operation. Therefore these patients were excluded.
† Despite increase of SBP after surgery, these patients were normotensive (SBP < 140 and DBP < 90 mmHg) on no or lower number of AHTN.
Abbreviations: SBP = Systolic Blood Pressure; No. = Number of; AHTN = Antihypertensive medications

cohort of patients operated for PA between 2010 and 2016. Although the majority of patients (58%) showed complete cure or clear improvement of hypertension after surgery, results also displayed beneficial clinical effects of surgery (i.e., reduction of blood pressure and/or antihypertensive medications) in a large proportion of patients with persistent hypertension after surgery. This is best highlighted within the 182 (42%) patients stratified as no clear success in which the benefits of surgery were less obvious. Unless postoperative persistent hypertension, 84% (32% of the total population) of patients within this subgroup still had any reduction in both blood pressure and antihypertensive medications. In addition, in 41% (15% of the total population) of patients stratified as no clear success this decrease in SBP was 10 mmHg or even more. As shown by Ettehad *et al.* this reduction should be considered clinically relevant because every 10 mmHg reduction in SBP leads to a risk reduction of 20% in major cardiovascular events, 17% in coronary heart disease, 27% in stoke, 28% in heart failure and 13% in all-cause mortality[19]. When combining these results it shows that, after adrenalectomy for PA, 90% of patients had any form of decrease in blood pressure and/or antihypertensive medications and in a minimum of 73% of patients we considered this decrease as certainly clinically significant.

Numerous studies targeted clinical success by describing proportions of patients with clinical cure and/or clinical improvement with a large heterogeneity in outcome criteria. In our study, 27% of patients showed clinical cure which is substantially lower compared to the 42%, 50% and 52% cure rates presented in recent reviews and meta-analyses[13-15]. However, the majority of studies included in these reviews and meta-analyses were small, single center and included patients over a wide range of years or even decades. Furthermore, because most studies mainly focused on describing proportions of patients with clinical cure and/or improvement

and potential prognostic factors they presented no or limited data on magnitude of decrease in blood pressure and antihypertensive medications making data regarding this subject scarce. However, recently results from the Primary Aldosteronism Surgery Outcome (PASO) investigators were published[18]. They presented clinical outcomes of adrenalectomy in a large and worldwide cohort of patients operated between 1994 and 2015. Although their primary goal was to establish consensus criteria for clinical and biochemical outcomes and describe prognostic factors for each outcome, they also displayed some data regarding the magnitude of decrease in blood pressure and antihypertensive medications within each outcome definition[18]. The PASO-investigators showed complete cure in 37% of patients which is lower compared to the earlier mentioned reviews and meta-analyses but still higher compared to our study. Although preoperative blood pressure measurements were comparable between studies, the PASO-investigators also showed a larger decrease in SBP and DBP compared to our results, 22 ± 22 mmHg vs. 17 ± 21 mmHg ($p<0.001$) and 11 ± 14 mmHg vs. 7 ± 14 mmHg ($p<0.001$), respectively. These differences may be attributable to dissimilar baseline characteristics. In accordance with earlier performed studies, the PASO-investigators identified younger age, female gender and lower body mass index (BMI) as predictors for a favorable clinical outcome[18,22,23]. Although age and distribution of gender were comparable between studies, BMI was lower within the PASO-study cohort, 27.8 ± 5.2 vs. 29.7 ± 6.0 ($p<0.001$), respectively[18]. Therefore, difference in BMI possible could be of influence. Because our study is representative for current clinical practice diagnostic modalities such as AVS or a confirmatory test were not routinely performed in all patients but performed based on center's preference and availability. Therefore, also patient selection could be a influencing factor. Another possible factor could be the substantial number of patients with relatively short follow-up after surgery within our cohort. In our cohort however, the period of follow-up was no significant influencing factor on the proportions of patients with cure, clear improvement and no clear success ($p=0.28$) or the decrease in SBP after surgery ($p=0.17$). Further comparison with the PASO-study was not possible due to a different definition of clear improvement and no clear success.

In contrast to earlier studies, we present clinical outcomes (including data on magnitude on blood pressure decrease) after adrenalectomy for PA in a large cohort only including patients operated within recent years. We chose to only include recently operated patients to minimize the potential risk on bias because of possible improvements in diagnosis, work-up, and treatment of PA due to innovation of guidelines, diagnostics modalities and surgical techniques over time. Furthermore, as indicated by Namekawa, *et al.*, increase in prevalence of obesity and diabetes mellitus over the last few decades potentially leads to a decrease in favorable clinical outcomes[24]. Likewise, due to the worldwide increase of hypertension within the last decades patients are less likely to achieve clinical cure of hypertension due to the background/essential hypertension which is not PA related[16]. Therefore, including patients over a wide range of years or even decades could lead to overestimation of surgical effect compared to results in current clinical practice. Another strength of this study is the worldwide and multicenter design that makes us believe that our results are representative for the western world.

Similar to almost all other studies regarding PA, the need for a retrospective design, mostly due to the low prevalence of PA, is one of the weaknesses of our study. Especially since this design made it impossible to use standardized procedures for blood pressure measurements such as performing out-of-office measurements in all patients. Also, the substantial number of patients with a relatively short follow-up is a potential shortcoming of this study. However, because excluding these patients with shorter follow-up could introduce selection bias and the duration of follow-up had no significant influence on our primary outcomes we chose to not exclude patients based on follow-up duration.

In conclusion, decreased blood pressure and reduced need for antihypertensive medications, in addition to biochemical cure, are clinically relevant beneficial effects of adrenalectomy in patients with PA. Although this study only shows complete clinical cure in approximately a quarter to one-third of patients, the majority of patients becomes normotensive on lower or equal use of antihypertensive medications. Moreover, also a large proportion of the patients with persistent hypertension after surgery still benefits from adrenalectomy given observed clinically relevant and significant reduction of blood pressure and antihypertensive use.

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SUPPLEMENT 1 GEOGRAPHIC STRATIFICATION OF BLOOD PRESSURE RELATED OUTCOMES

Variable	Total cohort (n=435)	Geographic regions			
		United States (n=248) (57%)	Europa (n=106) (24%)	Canada (n=42) (10%)	Australia (n=39) (9%)
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*
Preoperative					
Mean SBP (mmHg)	150 ± 20	151 ± 20	153 ± 19	141 ± 17	149 ± 15
Mean DBP (mmHg)	90 ± 13	89 ± 14	92 ± 12	87 ± 9	91 ± 12
Preoperative hypertension grade					
Grade 0	111 (25.5%)	58 (23.4%)	21 (19.8%)	22 (52.4%)	10 (25.6%)
Grade 1	180 (41.4%)	111 (45.2%)	42 (39.6%)	10 (23.8%)	16 (41.0%)
Grade 2	105 (24.1%)	54 (21.8%)	32 (30.2%)	9 (21.4%)	10 (25.6%)
Grade 3	39 (9.0%)	24 (9.7%)	11 (10.4%)	1 (2.6%)	3 (7.7%)
No. AHTN (/day)*	3 (0 – 8)	3 (0 – 8)	3 (0 – 7)	3 (1 – 6)	3 (0 – 5)
DDD (n=405)*	3.7 (0.0 – 25.3)	3.7 (0 – 25.3)	3.5 (0.0 – 13.7)	3.9 (1.0 – 11.0)	2.2 (0.0 – 8.7)
No. pills (/day) (n=407)*	3 (0 – 10)	3 (0 – 10)	3 (0 – 9)	3 (1 – 10)	4 (0 – 10)
Postoperative					
Mean SBP (mmHg)	133 ± 16	134 ± 18	135 ± 14	129 ± 13	129 ± 15
Mean DBP (mmHg)	83 ± 10	82 ± 11	84 ± 10	81 ± 9	82 ± 9
Postoperative hypertension grade					
Grade 0	269 (61.8%)	142 (57.3%)	68 (64.2%)	33 (78.6%)	26 (66.7%)
Grade 1	117 (26.9%)	74 (29.8%)	28 (26.4%)	6 (14.3%)	9 (23.1%)
Grade 2	41 (9.4%)	26 (10.5%)	8 (7.5%)	3 (7.1%)	4 (10.3%)
Grade 3	8 (1.8%)	6 (2.4%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
No. AHTN (/day)*	1.0 (0.0 – 6.0)	1 (0 – 6)	1 (0 – 6)	1 (0 – 3)	0 (0 – 3)
DDD (n=402)*	1.0 (0.0 – 11.7)	1.2 (0.0 – 11.7)	1.0 (0.0 – 7.0)	0.0 (0.0 – 5.0)	0.0 (0.0 – 6.0)
No. pills (/day) (n=407)*	1 (0 – 9)	1 (0 – 9)	1 (0 – 8)	1 (0 – 5)	0 (0 – 4)

SUPPLEMENT 1 (CONTINUED) GEOGRAPHIC STRATIFICATION OF BLOOD PRESSURE RELATED OUTCOMES

Preoperative-postoperative change					
Clinical success					
Cure	118 (27%)	54 (22%)	32 (30%)	15 (39%)	15 (39%)
Clear improvement	135 (31%)	77 (31%)	31 (29%)	11 (28%)	11 (28%)
No clear success	182 (42%)	117 (47%)	43 (41%)	13 (33%)	13 (33%)
SBP (mmHg)	17 ± 21	17 ± 23	18 ± 21	12 ± 16	20 ± 16
DBP (mmHg)	7 ± 14	7 ± 15	8 ± 13	6 ± 9	10 ± 12
SBP (%)	10.3% ± 13.2%	9.9% ± 14.2%	11.2% ± 12.4%	7.7% ± 10.4%	12.6% ± 10.4%
DBP (%)	7.0% ± 14.5%	6.3% ± 15.3%	7.5% ± 14.7%	6.6% ± 10.5%	9.7% ± 12.4%
No. AHTN (/day)*	2 (-3 – 6)	1 (-3 – 5)	2 (-3 – 6)	2 (0 – 4)	2 (-2 – 4)
No. AHTN (/day) (%)*	60% (-100% –100%)	50% (-100% – 100%)	63% (-100% – 100%)	75% (0% – 100%)	80% (-100% – 100%)
DDD (n=382)*	2.0 (-4.7 – 24.3)	2.0 (-4.7 – 24.3)	2.3 (-4.0 – 9.5)	2.8 (0.0 – 10.0)	1.7 (-3.0 – 6.4)
DDD (%)(n=382)*	73% (-400% – 100%)	65% (-256% – 100%)	73% (-400% – 100%)	100% (0% – 100%)	100% (-100% – 100%)
No. pills (/day) (n=388)*	2 (-3 – 8)	2 (-3 – 7)	2 (-3 – 6)	2 (0 – 8)	2 (-2 – 8)
No. pills (/day) (%) (n=388)*	67% (-200% – 100%)	50% (-200% – 100%)	67% (-100% – 100%)	100% (0% – 100%)	100% (-100% - 100%)

* Values not normally distributed given as medians (range)

Abbreviations: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; No. = Number of; AHTN = Antihypertensive medications; DDD= Defined Daily Dose.

CHAPTER

5

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

SURGERY 2019

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ABSTRACT

Background

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

Methods

Patients who underwent unilateral adrenalectomy for PA between 2010 and 2016 were included. Patients with missing data regarding preoperative or postoperative blood pressure or their defined daily dose (DDD) were excluded. According to the PASO 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 PASO 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 was due mainly to the cut-off 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 DDD.

Conclusion

Although introduction of the PASO consensus criteria induced substantial advancement in standardization of postoperative outcomes, this study suggests that there is room for improvement given observed limitations when the criteria were tested within our international cohort. In line, determining clinical success, especially in patients with opposing change in blood pressure and DDD, remains challenging.

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 that could even exceed 20% in case of 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). While 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 surgery include improvement in the control of blood pressure and a decrease in antihypertensive drug burden. Complete clinical success (i.e., normalization of blood pressure without the need for antihypertensive medications) ≤50%[14-18]. Patients without complete clinical success, however, may also benefit from surgery through reduction of blood pressure and/or medications with a subsequent decrease in morbidity and drug burden[19,20]. This decrease in systolic blood pressure (SBP) is potentially very important, because every decrease of 10 mmHg in SBP leads to a risk-reduction of 20% in cardiovascular morbidity and 13% in all-cause mortality in patients with hypertension. This risk-reduction is shown across various baseline blood pressure levels 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 hard 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 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 and/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 irrespective of potential concomitant biochemical cure[15].

Although the PASO consensus criteria are a valuable step towards global standardization of outcomes after surgery for PA, we hypothesized that these criteria might incorrectly classify patients as either partial or absent clinical success due to 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 ≥ 20 mmHg cut-off used to indicate clinically relevant change in SBP is too conservative[20]. Likewise, this relatively high cut-off could also imply that patients with a relatively high increase in SBP (e.g., 18 or 19 mmHg) would still be classified as 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 Europa, Canada, Australia and the United States.

METHODS

Patients

We performed a retrospective cohort study across 16 medical referral centers in Europa, Canada, Australia and the United States (Figure 1). Derivation of this study cohort has been extensively described 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 above the local reference range. Unilateral disease was diagnosed on computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or adrenal venous sampling (AVS) according to each center's preference and/or availability. Patients with missing preoperative or follow-up data regarding SBP, diastolic blood pressure (DBP), or DDD were excluded. The grade 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 head 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. Besides evaluation of the PASO consensus criteria we also investigated the influence of lowering the cut-off indicating a 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 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 due to 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 decrease in blood pressure patients were classified as absent clinical success. Unchanged blood pressure was defined as a difference in (preoperative vs. 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 vs. 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 due 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.

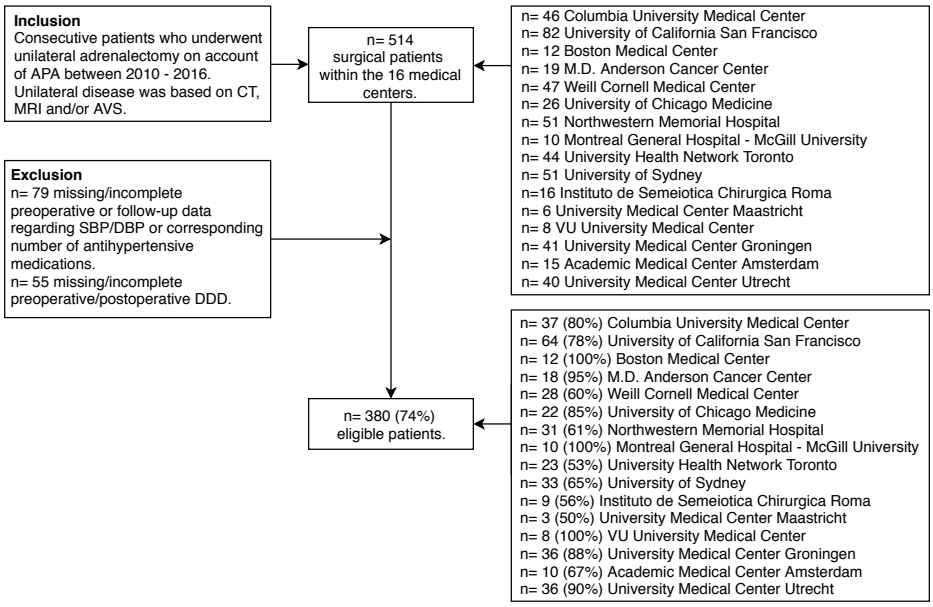
Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD) or median (Interquartile range (IQR)) The Chi-Square test and Fisher's 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 Kruskal-Wallis test 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 <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23.0 (IBM Corp, New York, USA) and figures were constructed using Graphpad Prism version 7.02 (GraphPad Software Inc, California, USA).

RESULTS

A total of 514 patients were identified in 16 participating referral centers and 380 (74%) were eligible for inclusion (Figure 1). The median number of included patients per center was 23[IQR 10 – 35]. Baseline characteristics of the cohort are presented in Table 1. 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.

FIGURE 1 FLOW-CHART OF INCLUDED PATIENTS FROM 16 REFERRAL CENTERS



Clinical success

Complete, partial, and absent clinical success were observed in 112 (30%), 183 (48%) and 85 (22%) patients, respectively (Table 2). 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 (Supplement 1).

In the total cohort, the mean SBP and DBP decreased by 16 (± 21) mmHg and 7 (± 14) mmHg after surgery (Table 2). 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 to patients with partial success, the postoperative decrease in SBP, DBP and DDD was comparable between both groups: 20 vs. 22 mmHg (p>0.999), 10 vs. 8 mmHg (p=>0.999) and 2.2 vs. 2.5 (p=0.124), respectively (Table 2). Postoperative 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=0.992) and patients with and without postoperative hyperaldosteronism (p=0.717).

Influence of AVS and follow-up duration 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=0.865). Hyperplasia on histology was shown in 16% vs.11% of patients with and without AVS (p=0.393).

TABLE 1 BASELINE CHARACTERISTICS OF 380 PATIENTS

Variable	Total cohort (n=380)	Clinical success			Overall p-value	Pairwise comparison p-values		
		Complete (n=112)(30%)	Partial (n=183)(48%)	Absent (n=85)(22%)		Complete vs. partial	Complete vs. absent	Partial vs. absent
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*				
Age at surgery (years)	50 ± 11	46 ± 10	52 ± 11	51 ± 11	**<0.001**	**<0.001**	**0.004**	0.859
Sex					**<0.001**	**<0.001**	**<0.001**	0.820
Female	165 (43%)	73 (65%)	62 (34%)	30 (35%)				
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]	**<0.001**	**<0.001**	**<0.003**	1.000
Body mass index (n=350)	30 ± 6	27 ± 5	30 ± 6	31 ± 5	**<0.001**	**<0.001**	**<0.001**	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]	**<0.001**	**<0.001**	**<0.001**	0.267
Hypokalemia (n=374)	275/374 (74%)	77/110 (70%)	140/179 (78%)	58/85 (68%)	0.139	0.117	0.791	0.080
History of CV events (n=377)	54/377 (14%)	6/111 (5%)	33/182 (18%)	15/84 (18%)	**0.006**	**0.002**	**0.005**	0.957
Diabetes (n=378)	50/378 (13%)	6/111 (5%)	32/182 (18%)	12/85 (14%)	**0.011**	**0.003**	**0.036**	0.477
Current smoker (n=367)	38/367 (10%)	8/109 (7%)	25/177 (14%)	5/81 (6%)	0.071	0.081	0.753	0.064
Hypercholesterolemia (n=377)	96/377 (26%)	11/111 (10%)	60/182 (33%)	25/84 (22%)	**<0.001**	**<0.001**	**<0.001**	0.602
FA history of HTN (n=298)	150/298 (50%)	34/82 (42%)	75/145 (52%)	41/71 (58%)	0.119	0.137	**0.045**	0.404
Preoperative mean systolic blood pressure with medication (mmHg)	150 ± 19	142 ± 16	157 ± 20	143 ± 15	**<0.001**	**<0.001**	1.000	**<0.001**
Preoperative mean diastolic blood pressure with medication (mmHg)	90 ± 13	88 ± 11	92 ± 14	87 ± 10	**0.001**	**0.014**	1.000	**0.005**
JNC/ESH hypertension grade based on blood pressure with medication					**<0.001**	**<0.001**	0.106	**<0.001**
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 (0%)				

* Values not normally distributed given as medians [IQR].

Abbreviations: HTN = hypertension; DDD = Defined Daily Dose; CV = Cardiovascular; FA = Family; JNC = Joint National Commission; ESH = European Society of Hypertension; ARR = Aldosterone to renin ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; AVS = Adrenal Venous Sampling; MRI = Magnetic Resonance Imaging; EPRA = Endoscopic Posterior Retroperitoneal Adrenalectomy; ELRA = Endoscopic Lateral Retroperitoneal Adrenalectomy; LTA = Laparoscopic Transabdominal Adrenalectomy.

TABLE 1 (CONTINUED) BASELINE CHARACTERISTICS OF 380 PATIENTS

Variable	Total cohort (n=380)	Clinical success			Overall p-value	Pairwise comparison p-values		
		Complete (n=112)(30%)	Partial (n=183)(48%)	Absent (n=85)(22%)		Complete vs. partial	Complete vs. absent	Partial vs. absent
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*				
Increased aldosterone level (n=353)	193/353 (55%)	66/104 (64%)	92/172 (54%)	35/77 (46%)	0.050	0.105	**0.016**	0.241
Suppressed renin level/activity (n=318)	214/318 (67%)	67/91 (74%)	102/157 (65%)	45/70 (64%)	0.312	0.158	0.202	0.912
ARR indicating PA (n=309)	292/309 (95%)	83/86 (97%)	145/154 (94%)	64/69 (93%)	0.574	0.422	0.468	0.690
Increased creatinine level (n=345)	60/345 (17%)	9/104 (9%)	39/165 (24%)	12/76 (16%)	**0.006**	**0.002**	0.141	0.166
CT performed (n=377)	330/377 (88%)	101/111 (91%)	157/182 (86%)	72/84 (86%)	0.419	0.226	0.249	0.904
AVS performed (n=379)	241/379 (64%)	70/111 (63%)	115/183 (63%)	56/85 (66%)	0.882	0.970	0.683	0.630
MRI performed (n=379)	64/379 (17%)	21/112 (19%)	33/182 (18%)	12/85 (12%)	0.356	0.894	0.182	0.187
Operative procedure					0.123	0.945	0.074	0.064
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%)	0.056	0.073	0.081	0.668
Histology (n=378)					**0.004**	**0.007**	**0.003**	0.199
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]	0.347	0.329	0.163	0.479

* Values not normally distributed given as medians [IQR].

Abbreviations: HTN = hypertension; DDD = Defined Daily Dose; CV = Cardiovascular; FA = Family; JNC = Joint National Commission; ESH = European Society of Hypertension; ARR = Aldosterone to renin ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; AVS = Adrenal Venous Sampling; MRI = Magnetic Resonance Imaging; EPRA = Endoscopic Posterior Retroperitoneal Adrenalectomy; ELRA = Endoscopic Lateral Retroperitoneal Adrenalectomy; LTA = Laparoscopic Transabdominal Adrenalectomy.

TABLE 2 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		
		Complete (n=112)(30%)	Partial (n=183)(48%)	Absent (n=85)(22%)		Complete vs. partial	Complete vs. absent	Partial vs. absent
	Number (%) or mean ± SD	*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	**<0.001**	**<0.001**	1.000	**<0.001**
Postoperative mean (mmHg)	133 ± 17	122 ± 9	136 ± 16	143 ± 18	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Pre-post Delta mean (mmHg)	16 ± 21	20 ± 17	22 ± 20	1 ± 19	**<0.001**	1.000	**<0.001**	**<0.001**
Pre-post Delta mean (%; ± SD)	10% ± 13%	13% ± 11%	13% ± 14%	0% ± 14%	**<0.001**	1.000	**<0.001**	**<0.001**
Diastolic blood pressure								
Preoperative mean (mmHg)	90 ± 13	88 ± 11	92 ± 14	87 ± 10	**0.001**	**0.014**	**1.000**	**0.005**
Postoperative mean (mmHg)	83 ± 10	78 ± 7	84 ± 11	86 ± 11	**<0.001**	**<0.001**	**<0.001**	0.428
Pre-post Delta mean (mmHg)	7 ± 14	10 ± 11	8 ± 15	1 ± 12	**<0.001**	**1.000**	**<0.001**	**<0.001**
Pre-post Delta mean (%; ± SD)	7% ± 14%	10% ± 13%	8% ± 14%	1% ± 14%	**<0.001**	0.691	**<0.001**	**<0.001**
JNC/ESH hypertension grade								
Preoperative					**<0.001**	**<0.001**	0.106	**<0.001**
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				
Postoperative					**<0.001**	**<0.001**	**<0.001**	**0.028**
Grade 0	236 (62%)	112 (100%)	89 (49%)	35 (41%)				
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]	**<0.001**	**<0.001**	**<0.001**	0.267
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]	**<0.001**	**<0.001**	**<0.001**	**<0.001**
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]	**<0.001**	0.625	**<0.001**	**<0.001**
Pre-post Delta DDD (%)*	74% [27 – 100]	100% [100 – 100]	67% [41 – 90]	20% [0 – 40]	**<0.001**	**<0.001**	**<0.001**	**<0.001**

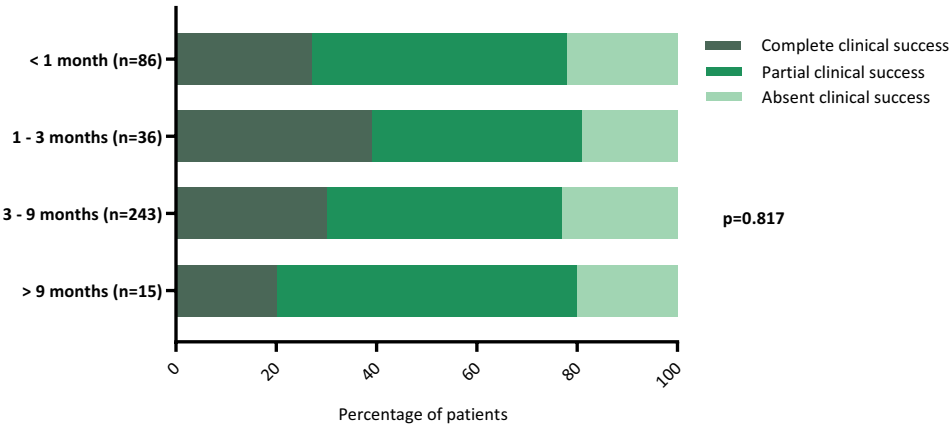
TABLE 2 (CONTINUED) EFFECT OF SURGERY ON BLOOD PRESSURE AND USE OF ANTIHYPERTENSIVE MEDICATIONS

Variable	Total cohort (n=380)	Clinical success			Overall p-value	Pairwise comparison p-value		
		Complete (n=112)(30%)	Partial (n=183)(48%)	Absent (n=85)(22%)		Complete vs. partial	Complete vs. absent	Partial vs. absent
	Number (%) or mean ± SD	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*	*Number (%) or mean ± SD*				
Number of pills per day (n=378)								
Preoperative (number/day)*	3 [2 – 5]	2 [1 – 3]	4 [2 – 5]	3 [2 – 5]	**<0.001**	**<0.001**	**<0.001**	0.339
Postoperative (number/day)*	1 [0 – 2]	0 [0 – 0]	1 [1 – 3]	2 [1 – 3.5]	**<0.001**	**<0.001**	**<0.001**	**0.014**
Pre-post Delta (number/day)*	2 [1 – 3]	2 [1 – 3]	2 [1 – 3]	1 [0 – 2]	**<0.001**	1.000	**<0.001**	**<0.001**
Pre-post Delta (%)*	67% [33 – 100]	100% [100 – 100]	56% [33 – 80]	25% [0 – 50]	**<0.001**	**<0.001**	**<0.001**	**<0.001**

* Values not normally distributed given as medians (IQR).

Abbreviations: JNC = Joint National Commission; ESH = European Society of Hypertension; DDD= Defined Daily Dose.

FIGURE 2 OUTCOMES AFTER UNILATERAL ADRENALECTOMY STRATIFIED BY MOMENT OF FOLLOW-UP



Patients with AVS did not show better outcomes regarding postoperative hypokalemia (p=0.474) and hyperaldosteronism (p=0.552). Final outcomes were assessed between 3 – 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=0.817)(Figure 2), change in SBP (p=0.332) nor change in DDD (p=0.132) 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, 30%, 48% and 22%, respectively. Also within this sub-selection of patients, no differences in rates of clinical success between patients with and without preoperative AVS were observed (p=0.959). Only selecting patients with 3 – 9 months follow-up and preoperative AVS resulted in comparable rates of complete, partial, and absent clinical success of 30%, 47%, and 23%, respectively.

Evaluation of the PASO consensus criteria

Table 3 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 three 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 SBP increase between 1 and 9 mmHg had 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. Within 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). Supplement 2 shows all patients classified as partial clinical success with incorrect or debatable classification. Within this subgroup, 10 patients had an increase in SBP of between 10 and 19

TABLE 3 DISTRIBUTION OF MAGNITUDE OF CHANGE IN BLOOD PRESSURE WITHIN COMPLETE, PARTIAL AND ABSENT CLINICAL SUCCESS

Postoperative change in systolic blood pressure		Clinical success						
			PASO criteria			When SBP ≥ 10 mmHg*		
		Total cohort (n=380)	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%)
	≥ 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 an absent clinical success when change of blood pressure would be defined as an increase or decrease of ≥ 10 mmHg in SBP compared to ≥ 20 mmHg used in the PASO consensus criteria.
Abbreviations: SBP = Systolic Blood Pressure.

mmHg indicating that these patients would have been classified as absent clinical success when using a ≥ 10 mmHg instead of ≥ 20 mmHg cut-off point indicating clinically relevant change in SBP (Table 3); 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 due to the opposing change in SBP and DDD (Supplement 2). One of the 15 patients with an increase of SBP of 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 absolute DDD value. Therefore, this patient should be classified as absent success (Supplement 2). 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 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 (Supplement 2). 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 (Supplement 3). Within this subgroup, 26 out of 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 4). When using a ≥ 10 mmHg change in SBP as cut-off point, these patients would be classified as partial clinical success (Tables 3 and 4). 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 correctly classified as absent success due to the high increase in DDD. Furthermore, 8 patients classified as absent success showed a decrease of SBP ≥ 20 mmHg, but were classified as absent clinical success because of an increase in DDD ≥ 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 a SBP increase ≥ 20 mmHg, the classification as absent success could be doubted because of large DDD decrease (Supplement 3).

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 countries 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 decrease in blood pressure and/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 cut-off 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 to 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 attributed to the greater baseline BMI and DDD within our cohort compared to 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 to 4.7]. Multiple studies also indicated gender, age, duration of hypertension, and

TABLE 4 PATIENTS CLASSIFIED AS ABSENT CLINICAL SUCCESS ACCORDING TO THE PASO CRITERIA BUT WITH CLINICALLY RELEVANT DECREASE IN BLOOD PRESSURE AND/OR ANTIHYPERTENSIVE MEDICATIONS

Preoperative		Postoperative			Change			Clinical success		
DDD	**BP (mmHg)**	**DDD**	**BP (mmHg)**	**FU (Months)**	**DDD**	**DDD (%)**	**SBP (mmHg)**	**PASO**	**SBP ≥10**	**Interpretation**
26 patients with 10 – 19 mmHg SBP decrease however classified as absent success due to 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*

* Patient should have been classified as partial success.

Abbreviations: DDD = Defined Daily Dose; BP = Blood Pressure; FU = Follow Up; SBP = Systolic Blood Pressure; PASO = Primary Aldosteronism Surgical Outcomes (criteria).

baseline SBP as predictors, however these characteristics were comparable between the two 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 (Supplement 1). 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, the preoperative work-up, 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 in all patients. Although outcomes were comparable between patients with and without preoperative AVS, this could still be of influence to the less rates of complete success. For instance, due to confounding by indication, AVS might have been performed in cases with a great risk of less favorable outcomes. Furthermore, because our cohort consisted of patients operated between 2010 and 2016 compared to 1995 and 2015 within the PASO cohort, the less rates of complete success could also be influenced by the worldwide increase in obesity and background/not PA-related hypertension over 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 final outcome assessment should be performed at 6 – 12 months after adrenalectomy. Unfortunately, our cohort was initiated prior to 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. Due to geographic distances and referral patterns in daily clinical practice, multiple centers were not able to achieve follow-up within this timeframe. In order 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 short follow-up (n=86) remains a limitation.

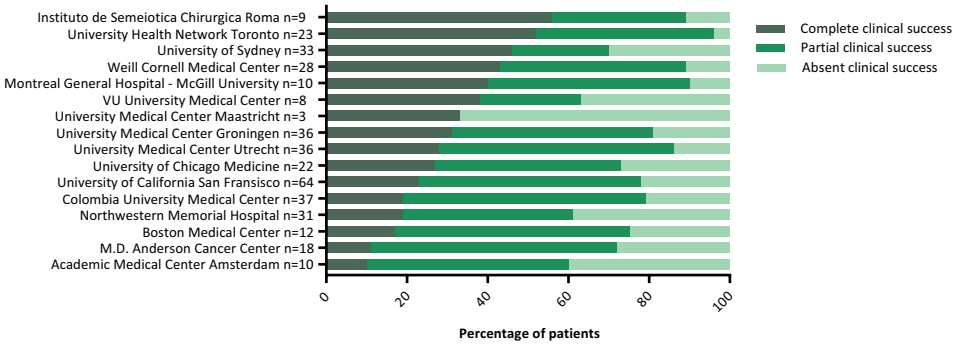
For use in day-to-day practice, the PASO criteria appeared to have some limitations when applied to our cohort. For instance, many patients achieved a 10 to 19 mmHg decrease in SBP with a substantial decrease in their absolute value of DDD. In our opinion, however, these patients clearly showed clinically relevant benefits from surgery and therefore, 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 reduction of SBP in patients with hypertension, we believe this cut-off should be decreased to ≥ 10 mmHg[20]. To our opinion, 30% of the patients which were classified as absent success according to the PASO criteria (7% of the complete cohort) would have been more accurately classified as partial success when the cut-off was adjusted to ≥ 10 mmHg (Table 4). Moreover, this change in cut-off minimizes the risk of classifying patients as partial success, based on a decrease in DDD, despite a clinically relevant increase in SBP (e.g., a 10 to 19 mmHg increase). Furthermore, the use of percentages instead of 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 result in a different decrease in blood pressure. Evidence from studies performed in patients with essential hypertension suggests an average 9 mmHg decrease in SBP at standard dose (1 DDD) of a antihypertensive drug. Therefore, one could suggest a ≥ 1 DDD cutoff to indicate change in antihypertensive medication which equals the proposed ≥ 10 mmHg cutoff to indicate change in SBP[30].[30] Determining the cut-off in DDD which equals the clinically relevant decrease in blood pressure, however, remains a major challenge, because of the complex relation between change in DDD and blood pressure. This is particularly important because two drugs at half dose add up to 1 DDD, but the decrease in blood pressure has proven to be significantly more than for one drug at 1 DDD[30]. Furthermore, patients with twice the standard dose (2 DDD) of a antihypertensive drug only achieve small additional decrease in SBP compared to 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 to 1 DDD of a different antihypertensive drug.

Similar to the majority of studies regarding PA, the need for a retrospective design, mostly due 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 over the day, instead of out-of-office 24-hour measurements which 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 work-up differs globally.

In conclusion, the PASO investigators introduced a substantial advancement 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 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 it is possible to properly investigate the true prognostic and discriminating factors which could be used for patient counseling.

SUPPLEMENT 1 OUTCOMES AFTER UNILATERAL ADRENALECTOMY STRATIFIED BY TREATMENT CENTER



SUPPLEMENT 2 PATIENTS CLASSIFIED AS PARTIAL CLINICAL SUCCESS BASED ON THE PASO CONSENSUS CRITERIA IN WHICH THIS CLASSIFICATION IS DEBATABLE

Preoperative		Postoperative			Change			Clinical success		
DDD	**BP (mmHg)**	**DDD**	**BP (mmHg)**	**FU (Months)**	**DDD**	**DDD (%)**	**SBP (mmHg)**	**PASO**	**SBP ≥ 10**	**Interpretation**
10 patients classified as partial success due to decrease of DDD ≥ 50% however with 10 – 19 mmHg increase of SBP										
8.3	170/80	3.0	186/95	< 1	- 5.3	- 64%	+ 16	Partial	Absent	Classification debatable
6.0	133/82	1.0	146/76	< 1	- 5.0	- 83%	+ 13	Partial	Absent	Classification debatable
3.3	147/76	0.0	159/94	< 1	- 3.3	- 100%	+ 12	Partial	Absent	Classification debatable
4.0	127/82	2.0	146/92	3 – 9	- 2.0	- 50%	+ 19	Partial	Absent	Classification debatable
3.8	122/79	0.2	136/85	1 – 3	- 3.6	- 96%	+ 14	Partial	Absent	Classification debatable
4.5	134/90	1.0	151/108	3 – 9	- 3.5	- 78%	+ 17	Partial	Absent	Classification debatable
9.5	139/87	1.0	154/104	3 – 9	- 8.5	- 89%	+ 15	Partial	Absent	Classification debatable
3.6	160/90	1.3	173/100	3 – 9	- 2.3	- 64%	+ 13	Partial	Absent	Classification debatable
4.2	132/85	0.0	144/95	3 – 9	- 4.2	- 100%	+ 12	Partial	Absent	Classification debatable
3.3	115/79	1.5	126/84	3 – 9	- 1.8	- 55%	+ 11	Partial	Absent	Classification debatable
1 patient classified as partial success due to decrease of DDD ≥ 50% however with 1 – 9 mmHg increase of SBP										
0.6	157/87	0.3	158/93	3 – 9	- 0.3	- 50%	+ 1	Partial	Partial	Incorrectly classified*
9 patients classified as partial success due to decrease of SBP however with increase in DDD										
3.0	143/86	4.0	117/84	3 – 9	+ 1.0	+ 33%	- 26	Partial	Partial	Classification debatable
5.8	182/104	7.0	147/97	3 – 9	+ 1.2	+ 20%	- 35	Partial	Partial	Classification debatable
5.3	154/88	6.3	116/70	3 – 9	+ 1.0	+ 19%	- 38	Partial	Partial	Classification debatable
3.3	190/120	3.8	129/80	3 – 9	+ 0.5	+ 15%	- 61	Partial	Partial	Classification debatable
2.7	171/99	3.0	140/80	< 1	+ 0.3	+ 13%	- 31	Partial	Partial	Classification debatable
3.2	160/75	3.5	139/75	3 – 9	+ 0.3	+ 11%	- 21	Partial	Partial	Classification debatable
5.4	200/101	6.0	134/87	3 – 9	+ 0.6	+ 10%	- 66	Partial	Partial	Classification debatable
2.2	164/76	2.3	120/72	3 – 9	+ 0.1	+ 8%	- 44	Partial	Partial	Classification debatable
4.8	152/85	5.1	121/67	< 1	+ 0.3	+ 8%	- 31	Partial	Partial	Classification debatable

* Patient should have been classified as absent success.

Abbreviations: DDD = Defined Daily Dose; BP = Blood Pressure; FU = Follow Up; SBP = Systolic Blood Pressure; PASO = Primary Aldosteronism Surgical Outcomes (criteria).

SUPPLEMENT 3 PATIENTS CLASSIFIED AS ABSENT CLINICAL SUCCESS BASED ON THE PASO CONSENSUS CRITERIA IN WHICH THIS CLASSIFICATION IS INCORRECT OR DEBATABLE

Preoperative		Postoperative			Change			Clinical success		
DDD	BP (mmHg)	DDD	BP (mmHg)	FU (Months)	DDD	DDD (%)	SBP mmHg)	PASO	SBP ≥ 10	Interpretation
26 patients with 10 – 19 mmHg SBP decrease however classified as absent success due to 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*

SUPPLEMENT 3 (CONTINUED) PATIENTS CLASSIFIED AS ABSENT CLINICAL SUCCESS BASED ON THE PASO CONSENSUS CRITERIA IN WHICH THIS CLASSIFICATION IS INCORRECT OR DEBATABLE

Preoperative		Postoperative			Change			Clinical success		
DDD	**BP (mmHg)**	**DDD**	**BP (mmHg)**	**FU (Months)**	**DDD**	**DDD (%)**	**SBP mmHg)**	**PASO**	**SBP ≥ 10**	**Interpretation**
8 patients classified as absent success due to increase in DDD ≥ 50% however with decrease in SBP ≥ 20 mmHg										
1.7	166/98	6.0	144/92	< 1	+ 4.3	+ 256%	- 22	Absent	Absent	Classification debatable
0.0	154/97	2.0	129/79	< 1	+ 2.0	+ 100%	- 25	Absent	Absent	Classification debatable
0.5	143/84	1.3	118/67	3 – 9	+ 0.8	+ 150%	- 25	Absent	Absent	Incorrectly classified*
0.0	175/105	3.0	150/80	3 – 9	+ 3.0	+ 100%	- 25	Absent	Absent	Classification debatable
1.8	152/90	3.0	127/76	1 – 3	+ 1.2	+ 71%	- 25	Absent	Absent	Classification debatable
1.0	144/94	2.3	118/77	3 – 9	+ 1.3	+ 133%	- 26	Absent	Absent	Classification debatable
1.0	149/90	5.0	121/62	3 – 9	+ 4.0	+ 400%	- 27	Absent	Absent	Classification debatable
0.6	174/96	1.0	125/70	3 – 9	+ 0.4	+ 67%	- 49	Absent	Absent	Incorrectly classified*
6 patients classified as absent success due to increase in SBP ≥ 20 mmHg however with substantial decrease in DDD										
3.3	147/79	0.0	173/94	< 1	- 3.3	- 100%	+ 26	Absent	Absent	Classification debatable
7.3	137/68	1.3	162/73	< 1	- 6.0	- 82%	+ 25	Absent	Absent	Classification debatable
7.0	131/90	2.0	152/104	3 – 9	- 5.0	- 71%	+ 21	Absent	Absent	Classification debatable
4.8	120/70	0.0	140/80	3 – 9	- 4.8	- 100%	+ 20	Absent	Absent	Classification debatable
3.7	108/60	0.0	141/80	< 1	- 3.7	- 100%	+ 33	Absent	Absent	Classification debatable
13.3	103/95	3.3	147/96	1 – 3	- 10.0	- 75%	+ 44	Absent	Absent	Classification debatable

* Patient should have been classified as partial success.

Abbreviations: DDD = Defined Daily Dose; BP = Blood Pressure; FU = Follow Up; SBP = Systolic Blood Pressure; PASO = Primary Aldosteronism Surgical Outcomes (criteria).

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CHAPTER

6

Validation of the Aldosteronoma Resolution Score within current clinical practice

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ABSTRACT

Introduction

Complete resolution of hypertension after adrenalectomy for primary aldosteronism is far from a certainty. This stresses the importance for adequate preoperative patient counseling. The Aldosteronoma Resolution Score (ARS) is a simple and easy to use prediction model only including 4 variables: ≤ 2 antihypertensive medications, body mass index ≤ 25 kg/m2, duration of hypertension ≤ 6 years and female sex. However, because the model was developed and validated within the United States (US) over a decade ago the applicability in modern practice and outside of the US in questionable. Therefore, we aimed to validate the ARS in current clinical practice within an international cohort.

Material and Method

Patients who underwent unilateral adrenalectomy, between 2010 and 2016, in 16 medical centers from the United States (US), Europe (EU), Canada (CA) and Australia (AU) were included. Resolution of hypertension was defined as normotension without antihypertensive medications.

Results

In total 514 patients underwent adrenalectomy and 435 (85%) patients were eligible. Resolution of hypertension was achieved in 27% patients within the total cohort and in 22%, 30%, 40% and 38% of patients within US, EU, CA and AU, respectively (p=0.015). The area under the curve (AUC) for the complete cohort was 0.751. Geographic validation displayed a AUC within the US, EU, CA and AU of 0.782, 0.681, 0.811 and 0.667, respectively.

Discussion

The ARS is an easy to use prediction model with a moderate to good predictive performance within current clinical practice. The model showed the highest predictive performance within North America, but potentially has less predictive performance in EU and AU.

INTRODUCTION

Primary aldosteronism (PA) is the most common form of secondary hypertension with an estimated prevalence between 5% and 20% depending on the severity of hypertension[1-4]. PA leads to morbidity and mortality through the effects of hypertension and aldosteronism itself on critical organs[5-8]. Therefore, the ultimate goal of treatment is resolution of both. Bilateral adrenal hyperplasia is treated medically while patients with an unilateral aldosterone producing adenoma (APA) are preferably treated by unilateral adrenalectomy[9-12].

Cure of aldosteronism is reported in the majority of patients after adrenalectomy for APA[13-15]. However, resolution of hypertension, also called cure of hypertension (i.e., a normotensive patient without antihypertensive medications), is far from a certainty. In the past, resolution rates were estimated around 50%[13,14,16]. However, recently Williams *et al*. showed less optimistic results by presenting a 37% resolution rate within a large, international and well-executed study[15]. Moreover, recently our own study group also published on blood pressure related outcomes after surgery for PA and we presented an even lower resolution rate of 27 – 30%[17,18]. This stresses the importance for adequate patient counseling and expectation management before performing an operation. To do this, clinicians need a user-friendly and reliable prediction model.

In 2008, Zarnegar *et al*. proposed the Aldosteronoma Resolution Score (ARS) as a practical prediction model for resolution of hypertension[19]. The model is very easy to use because it only includes 4 dichotomous preoperative patient/disease characteristics associated with a high probability of resolution of hypertension: taking ≤ 2 number of antihypertensive medications (AHTN) (2 points), body mass index (BMI) ≤ 25 kg/m2 (1 point), duration of hypertension ≤ 6 years (1 point) and female sex (1 point). Based on the combined scores three likelihood ratios for resolution of hypertension were identified: low (0 – 1), medium (2 – 3) and high (4 – 5) with corresponding likelihoods of resolution of 28%, 46% and 75%, respectively. The area under the curve (AUC) was 0.913[19].

In the past, validation of the ARS showed contradicting results between studies and was frequently performed within small and single country or single center study populations. In addition, these studies often included patients treated over several decades due to the low incidence of disease. Furthermore, the ARS was developed over a decade ago and, because of the improvement of diagnostic modalities and guidelines, patient care has made substantial progress over the years. This underscores the need to evaluate the clinical applicability and usefulness of the ARS in the current clinical APA population, especially because the performance of a prediction model may change over time[20-22]. In addition, since the prediction model was developed within the United States (US), the ARS is likely to have lower predictive value outside of the US which questions the generalizability of the ARS worldwide. Therefore, we aimed to be the first to validate the ARS in current clinical practice and expand this geographically in a worldwide cohort of patients who had adrenalectomy between 2010 and 2016.

METHODS

Patients and data collection

We performed a retrospective cohort study across 16 medical centers in the US, Europe (EU), Canada (CA) and Australia (AU)(Figure 1). Derivation of this cohort has been described before[17]. In brief, all patients who underwent unilateral adrenalectomy between 2010 and 2016 for APA were included. Because we aimed to make our study representative for current real life clinical practice no strict inclusion or exclusion criteria were used regarding screening, case confirmation or subtype testing. Laterality of disease was based on Computerized Tomography (CT) and/or Magnetic Resonance Imaging (MRI) and/or Adrenal Venous Sampling (AVS). In general, biochemical evidence for PA was based on an elevated aldosterone-to-renin ratio (ARR) indicating PA. Patients with missing preoperative or follow-up data regarding systolic blood pressure (SBP), diastolic blood pressure (DBP) or corresponding number of AHTN were excluded (Figure 1). Institutional review board approval was obtained in all participating centers.

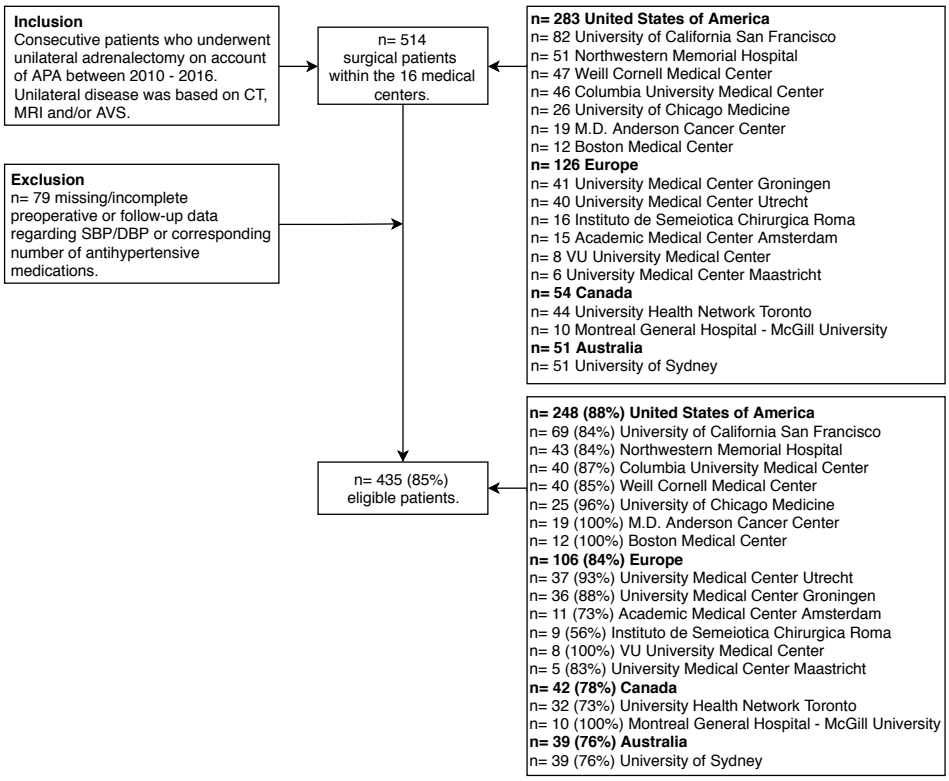
Definitions and outcomes

Resolution of hypertension was defined as a postoperative normotensive patient (i.e., SBP <140 mmHg and DBP <90 mmHg) without antihypertensive medications. Office blood pressure measurements were performed during outpatient visitation. Number of AHTN was defined as the number of different antihypertensive medications used. The defined daily dose (DDD) was calculated with the World Health Organization Anatomical Therapeutic Chemical/DDD Index 2017 (see https://www.whocc.no/atc_ddd_index/). When a medication stop was performed due to laboratory measurements, for example prior to the ARR, the number of AHTN, DDD and corresponding blood pressure before discontinuation were used. Biochemical data were classified as elevated/suppressed when values were above/below the local reference range. Hypokalemia was defined as either a potassium level below the local reference ranges or the use of potassium supplementation. The predictive accuracy of the ARS was reported as the proportion of patients with resolution for every ARS subgroup. Geographic validation was performed after division of the cohort in to 4 geographic regions: US, EU, CA and AU[20-22]. The goal was to assess resolution of hypertension at follow-up closest to 6 months after adrenalectomy.

Statistical Analysis

The Chi-Square test and Fisher's exact test were used to analyze group differences for categorical variables. For comparisons of continuous variables between multiple groups, One-Way ANOVA was used for normally distributed data and Kruskal-Wallis Test for not normally distributed data. A p-value of <0.05 was considered statistically significant. Multiple variables used as predictors in the ARS had missing values. To be able to calculate the ARS in all patients, these variables were imputed using multiple imputation with 20 imputed datasets[23]. The duration of hypertension and BMI were missing in 16% and 8% of patients, respectively. Gender and number of AHTN were known in all patients (Table 1). The primary

FIGURE 1 FLOW-CHART OF INCLUDED PATIENTS



Abbreviations: APA = Aldosterone Producing Adenoma; CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; AVS = Adrenal Venous Sampling; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

endpoint of this study (i.e., resolution of hypertension) was known in all patients. Pooled negative predictive values (NPV), positive predictive values (PPV) and AUCs of the ARS for resolution were calculated. Statistical analysis was performed using SPSS version 25.0 (IBM Corp, New York, USA) and figures were constructed using Graphpad Prism version 7.02 (GraphPad Software Inc, California, USA).

RESULTS

Baseline characteristics are shown in Table 1. Five hundred-fourteen patients underwent adrenalectomy and 435 (85%) patients were eligible for analysis. Two hundred forty-eight (57%), 106 (24%), 42 (10%) and 39 (9%) patients were included from US, EU, CA and AU, respectively. Patients within the US had a BMI of 30.4 ± 6.7, which was significantly higher compared to patients from the EU, CA or AU. The other predictors used within the ARS were

TABLE 1 BASELINE CHARACTERISTICS OF THE COMPLETE COHORT AND STRATIFIED BY REGION

Variable	All patients (n=435)	United States (n=248) (57%)	Europe (n=106) (24%)	Canada (n=42) (10%)	Australia (n=39) (9%)	Overall p-value
	Number (%) or mean ±SD	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	
Age at surgery (years)	50.7 ± 11.4	50.0 ± 11.6	51.3 ± 10.3	52.5 ± 11.6	51.2 ± 12.4	0.485
Female	186 (43%)	113 (46%)	37 (35%)	19 (45%)	17 (44%)	0.310
Duration of HTN (years)(n=366)*	9 (0 – 42)	10 (0 – 42)	9 (1 – 33)	7 (1 – 40)	6 (0 – 30)	0.220
Body mass index (n=402)	29.7 ± 6.1	30.4 ± 6.7	28.9 ± 5.1	28.9 ± 4.6	27.5 ± 4.7	**0.032**
No. AHTN*	3 (0 – 8)	3 (0 – 8)	3 (0 – 7)	3 (1 – 6)	3 (0 – 5)	0.598
DDD (n=405)*	3.7 (0.0 – 25.3)	3.7 (0.0 – 25.3)	3.5 (0.0 – 13.7)	3.9 (1.0 – 11.0)	2.2 (0.0 – 8.7)	0.290
Preoperative mean SBP (mmHg)	150 ± 20	151 ± 20	154 ± 19	140 ± 17	149 ± 15	**0.002**
Preoperative mean DBP (mmHg)	90 ± 13	89 ± 14	92 ± 12	87 ± 9	91 ± 12	0.150
Hypokalemia (n=429)	317 (74%)	185 (76%)	77 (73%)	29 (69%)	26 (67%)	0.481
Elevated aldosterone level (n=408)	225 (55%)	124 (52%)	56 (57%)	23 (58%)	22 (69%)	0.316
Suppressed renin level/activity (n=370)	245 (66%)	138 (64%)	60 (70%)	31 (86%)	16 (52%)	**0.015**
ARR indicating PA (n=361)	341 (95%)	202 (93%)	74 (96%)	36 (100%)	29 (94%)	0.342
Elevated creatinine level (n=392)	71 (18%)	39 (19%)	19 (18%)	7 (17%)	6 (15%)	0.956
CT performed (n=432)	378 (88%)	214 (87%)	89 (84%)	37 (88%)	38 (97%)	0.191
AVS performed (n=434)	278 (64%)	160 (65%)	59 (56%)	28 (67%)	31 (80%)	0.187
MRI performed (n=434)	72 (17%)	47 (19%)	16 (15%)	4 (10%)	5 (13%)	0.369
Confirmatory test performed	143 (33%)	38 (27%)	80 (56%)	7 (17%)	18 (46%)	**<0.001**
Surgical procedure						**<0.001**
EPRA	171 (39%)	79 (32%)	44 (42%)	27 (64%)	21 (54%)	
ELRA	65 (15%)	55 (22%)	8 (8%)	0 (0%)	2 (5%)	
LTA	198 (46%)	113 (46%)	54 (51%)	15 (36%)	16 (41%)	
Open	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	
Tumor laterality						0.916
Left	260 (60%)	149 (60%)	64 (60%)	23 (55%)	24 (62%)	
Right	175 (40%)	99 (40%)	42 (40%)	19 (45%)	15 (38%)	

TABLE 1 (CONTINUED) BASELINE CHARACTERISTICS OF THE COMPLETE COHORT AND STRATIFIED BY REGION

Variable	All patients (n=435)	United States (n=248) (57%)	Europe (n=106) (24%)	Canada (n=42) (10%)	Australia (n=39) (9%)	Overall p-value
	Number (%) or mean ±SD	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	*Number (%) or mean ±SD*	
Histology (n=434)						0.058
Adenoma	362 (84%)	209 (85%)	80 (76%)	39 (93%)	34 (87%)	
Hyperplasia	58 (13%)	34 (14%)	20 (19%)	1 (2%)	3 (8%)	
Adenoma/hyperplasia	13 (3%)	4 (2%)	5 (5%)	2 (5%)	2 (5%)	
Follow up after surgery						**<0.001**
< 1 month	101 (23%)	95 (38%)	3 (3%)	3 (7%)	0 (0%)	
1 – < 3 months	39 (9%)	19 (8%)	11 (10%)	9 (21%)	0 (0%)	
3 – 9 months	278 (64%)	131 (53%)	81 (76%)	27 (64%)	39 (100%)	
> 9 – 18 months	17 (4%)	3 (1%)	11 (10%)	3 (7%)	0 (0%)	

* Values not normally distributed given as medians (range)

Abbreviations: HTN = hypertension; No. AHTN = Number of antihypertensive medications; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ARR = Aldosterone-to-Renin-Ratio; PA = Primary Aldosteronism; CT = Computerized Tomography; AVS = Adrenal Venous Sampling; MRI = Magnetic Resonance Imaging; EPRA = Endoscopic Posterior Retroperitoneal Adrenalectomy; ELRA = Endoscopic Lateral Retroperitoneal Adrenalectomy; LTA = Laparoscopic Transabdominal Adrenalectomy.

FIGURE 2 RATES OF RESOLUTION OF HYPERTENSION STRATIFIED BY REGION AND MEDICAL CENTER

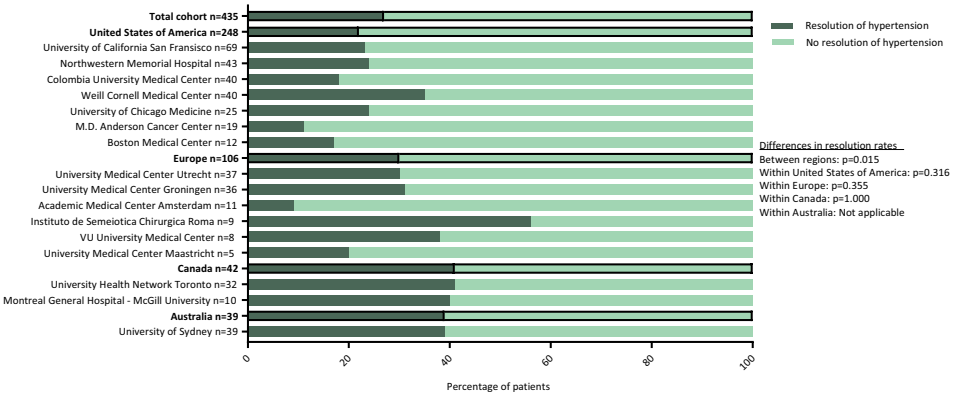
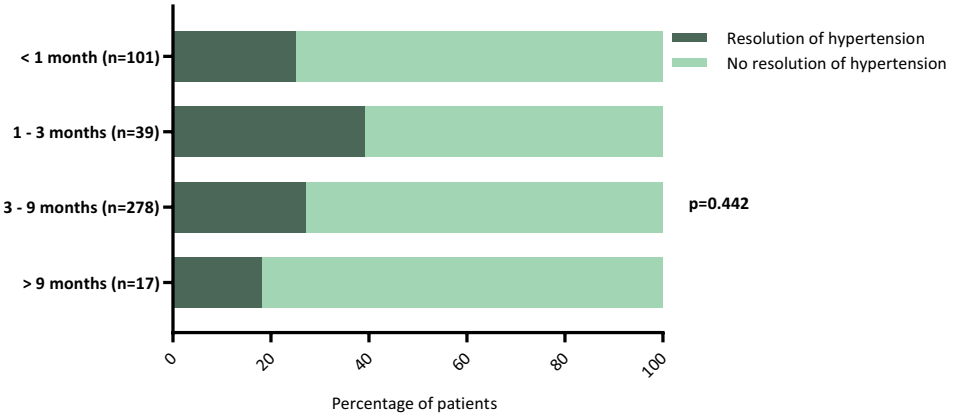


FIGURE 3 RATES OF RESOLUTION OF HYPERTENSION STRATIFIED BY DURATION OF FOLLOW-UP



comparable between the different regions. Furthermore, CT and AVS were performed in 88% and 64% of patients and the use of these modalities was comparable between the regions. A confirmatory test was more frequently performed within EU and AU compared to the US and CA, 56% and 46% vs. 27% and 17%, respectively. In 64% of patients follow-up was performed approximately 6 months after surgery (range 3 – 9 months).

Resolution of hypertension was achieved in 118 (27%) patients within the total cohort and in 54 (22%), 32 (30%), 17 (40%) and 15 (38%) patients within US, EU, CA and AU, respectively (p=0.015). No differences in resolution rates were found between the centers within each of the 4 regions (Figure 2). Patients with and without preoperative AVS achieved resolution of hypertension in 31% and 28%, respectively (p=0.524). No significant differences were seen

TABLE 2 DICHOTOMOUS VARIABLES USED FOR THE ARS STRATIFIED BY REGION

Variables	All patients (n=435)	United States (n=248) (57%)	Europe (n=106) (24%)	Canada (n=42) (10%)	Australia (n=39) (9%)	Overall p-value
	Number (%)	*Number (%)*	*Number (%)*	*Number (%)*	*Number (%)*	
No. antihypertensive medications ≤ 2	180 (41%)	97 (39%)	49 (46%)	19 (45%)	15 (39%)	0.584
Body mass index ≤ 25 kg/m^2*	98 (23%)	57 (23%)	20 (19%)	11 (26%)	10 (26%)	0.603
Duration of HTN ≤ 6 years*	171 (39%)	91 (37%)	44 (42%)	18 (43%)	18 (46%)	0.499
Female	186 (43%)	113 (46%)	37 (35%)	19 (45%)	17 (44%)	0.310

* Including imputed data.
Abbreviations: No. = Number of; HTN = Hypertension.

between patients with and without a confirmatory test (p=0.232). The rates of resolution of hypertension were comparable between the 4 follow-up periods (p=0.442)(Figure 3) and between patients with < 1 month and 3 – 9 months follow-up (p=0.400). Postoperative potassium and aldosterone were measured in 95% and 64% of patients, showing hypokalemia and hyperaldosteronism in 12% and 4%, respectively. Biochemical outcomes stratified per region are presented in supplement 1.

Validation of the ARS in current clinical practice

There were no significant differences in the dichotomous ARS variables between the geographic regions (Table 2). ARS 0, 1, 2, 3, 4 and 5 were observed in 25%, 19%, 20%, 20%, 10% and 6% of patients, respectively (Table 3). These scores were comparable between the 4 regions (p=0.484). Within the complete cohort, assessment of the proportion of patients with resolution of HTN within each ARS showed a likelihood of 7% in case of ARS 0 and 84% in case of ARS 5. This corresponded to a NPV of 93% for ARS 0 and a PPV of 84% for ARS 5. The corresponding AUC was 0.751 (95% CI 0.699 – 0.802). When using the likelihood levels as proposed by Zarnegar *et al.,* ARS 0 – 1 (low), ARS 2 – 3 (medium) and ARS 4 – 5 (high) showed predictive accuracies of 11%, 33% and 59%, respectively[19]. The corresponding AUC for this categorical ARS was 0.718 (95% CI 0.664 – 0.772). Geographic validation showed a NPV of 96% for ARS 0 and a PPV of 79% for ARS 5 with a AUC of 0.782 (95% CI 0.714 – 0.851) within the US. In EU a NPV of 88%, PPV of 75% and AUC of 0.681 (95% CI 0.571 – 0.792) were observed. Furthermore, a NPV, PPV and AUC of 90%, 100% and 0.811 (95% CI 0.678 – 0.943) and 60%, 67% and 0.667 (95% CI 0.483 – 0.851) were found for CA and AU, respectively.

TABLE 3 GEOGRAPHIC VALIDATION OF THE ALDOSTERONOMA RESOLUTION SCORE

	All patients (n=435)			United States (n=248)(57%)		
Variable	**Total**	**Resolution (n=118)(27%)**	**AUC (95% CI)**	**Total**	**Resolution (n=54)(22%)**	**AUC (95% CI)**
ARS (Cont.)			0.751			0.782
0	110/435 (25%)	8/110 (7%)	(0.699 – 0.802)	68/258 (27%)	3/68 (4%)	(0.714 – 0.851)
1	84/435 (19%)	14/84 (17%)		50/258 (20%)	5/50 (10%)	
2	85/435 (20%)	20/85 (24%)		45/258 (19%)	8/45 (18%)	
3	86/435 (20%)	35/86 (41%)		40/258 (16%)	15/40 (38%)	
4	45/435 (10%)	20/45 (44%)		31/258 (12%)	12/31 (39%)	
5	25/435 (6%)	21/25 (84%)		14/258 (5%)	11/14 (79%)	
ARS (Cat.)			0.718			0.747
0 – 1	194/435 (44%)	22/194 (11%)	(0.664 – 0.772)	118/258 (47%)	8/118 (7%)	(0.674 – 0.820)
2 – 3	171/435 (40%)	55/171 (32%)		85/258 (35%)	24/85 (28%)	
4 – 5	70/435 (16%)	41/70 (59%)		45/258 (17%)	23/45 (51%)	

	Europe (n=106)(24%)			Canada (n=42)(10%)		
Variable	**Total**	**Resolution (n=32)(30%)**	**AUC (95% CI)**	**Total**	**Resolution (n=17)(40%)**	**AUC (95% CI)**
ARS			0.681			0.811
0	25/106 (24%)	3/25 (12%)	(0.571 – 0.792)	10/42 (24%)	1/10 (10%)	(0.678 – 0.943)
1	20/106 (19%)	5/20 (25%)		5/42 (12%)	0/5 (0%)	
2	22/106 (21%)	6/22 (27%)		10/42 (24%)	5/10 (50%)	
3	27/106 (25%)	11/27 (41%)		12/42 (26%)	6/10 (60%)	
4	8/106 (7%)	4/8 (50%)		1/42 (2%)	1/1 (100%)	
5	4/106 (4%)	3/4 (75%)		4/42 (10%)	4/4 (100%)	
ARS (Cat.)			0.649			0.815
0 – 1	45/106 (43%)	8/45 (18%)	(0.534 – 0.764)	15/42 (36%)	1/10 (10%)	(0.686 – 0.944)
2 – 3	49/106 (46%)	17/49 (35%)		22/42 (52%)	11/17 (65%)	
4 – 5	12/106 (11%)	7/12 (58%)		5/42 (12%)	5/5 (100%)	

	Australia (n=39)(9%)		
Variable	**Total**	**Resolution (n=15)(38%)**	**AUC (95% CI)**
ARS			0.667
0	8/39 (21%)	2/8 (40%)	(0.483 – 0.851)
1	10/39 (26%)	3/10 (30%)	
2	7/39 (18%)	2/7 (29%)	
3	7/39 (18%)	3/7 (43%)	
4	4/39 (10%)	3/4 (75%)	
5	3/39 (8%)	2/3 (67%)	
ARS (Cat.)			0.653
0 – 1	18/39 (46%)	5/18 (28%)	(0.469 – 0.836)
2 – 3	14/39 (36%)	5/14 (36%)	
4 – 5	7/39 (18%)	5/7 (71%)	

Abbreviations: ARS = Aldosteronoma Resolution Score; Cont. = Continuous scale; Cat. = Categorical; AUC = Area Under the Curve; CI = Confidence Interval

DISCUSSION

This study validated the ARS within a worldwide cohort of patients which is representative for current clinical practice. Validation of the ARS within the complete cohort showed a moderate to good AUC of 0.751. Furthermore, the AUC was 0.782 within current US APA population. Although this prognostic accuracy was lower compared to the original data presented by Zarnegar *et al.* (AUC 0.913), it could still be considered as moderate to good prognostic performance[19]. Further geographic validation of the ARS displayed a comparable prognostic value within CA (AUC 0.811), but lower prognostic performance within EU (AUC 0.681) and AU (AUC 0.667) potentially indicating limited generalizability of the ARS outside the North American population.

The ARS, as introduced in 2008 by Zarnegar *et al.*, is a user-friendly model to predict the likelihood of resolution of hypertension after adrenalectomy for PA[19]. Because the ARS was developed in the US within a single center cohort of 100 patients over a decade ago, it is essential to confirm that the model also predicts well in, and thus is generalizable to, APA patients which were treated within other institutions or in different clinical settings and diagnostic protocols[20-22]. This underscores the need for the evaluation of clinical applicability and usefulness of the ARS in the current clinical APA population, especially because the performance of a prediction model may change over time[20-22]. In the past, validation of the prediction model by others showed contradicting results, however these studies were single center or country and frequently had small sample size[24-26]. Therefore, we chose to perform validation of the ARS within our large and worldwide cohort of patients, which at this time is the best available population to truly evaluate the generalizability in current real life clinical practice. The results showed a lower, but still moderate to good, predictive performance of the ARS within the US (AUC 0.782) compared to the development dataset AUC 0.913[19]. Usually, this is expected because prediction models are likely to show optimistic results within the development dataset, because all development techniques are prone to produce ''overfitted'' models, especially when small datasets (with limited numbers of outcomes) are used[20-22]. In line, performance is often poorer in validation studies because of differences in case-mix and domains. Because our study contained almost 250 patients from the US from 7 different medical centers, we believe this study shows a good generalizability of the ARS within the US. Furthermore, results also showed a decent performance within CA (AUC 0.811). Therefore, these results indicate that the ARS could be an easy to use tool for clinicians from North America to use during patient counseling. Nevertheless, results showed a lower predictive performance of the ARS within the EU (AUC 0.681) and AU (AUC 0.667) demonstrating the potential limited transportability of the model to other countries or continents worldwide. Although this is potentially due to differences in case mix and baseline characteristics, our results surprisingly showed no clear differences within the 4 predictors used for the ARS or individual ARSs between the 4 regions. For instance, although patients from the US had significant higher BMI compared to the other regions this did not result in a lower proportion of patients with BMI ≤ 25 kg/m^2 or more patients with a low ARS (Table 2).

We observed resolution of HTN in 27% of patients which is lower compared to the 42%, 50% and 52% presented in reviews or meta-analyses and the 37% presented within another worldwide study by Williams *et al.*[13-16]. Most likely this difference is multifactorial. For instance, these earlier studies included patients treated over several decades ago and therefore the lower rates of resolution could be influenced by the worldwide increase in obesity and background/not PA related hypertension over the years[27-29]. Furthermore, because we meant our results to be representative for current clinical practice the preoperative work-up, including screening, case confirmation and subtype testing, was not as stringent as in other studies. Potentially this led to less favorable outcomes compared to studies only including patients who, for instance, underwent AVS and thus represent more selected study populations. Although our results showed no difference in resolution rates between patients with and without preoperative AVS we cannot rule out that AVS truly does not improve outcomes because our cohort and study design are subject to confounding by indication. Further blood pressure related outcomes and the potential benefits of surgery for patients without resolution of hypertension (i.e., reduction of blood pressure and antihypertensive medications) within this cohort were described in detail before[17,18].

When comparing rates of resolution between the 4 regions, results showed a significantly lower resolution rate within the US (22%) compared to EU (30%), CA (40%) and AU (38%). Besides a significantly higher mean BMI within the US, another potential influence on the lower resolution rate could be the difference in preoperative work-up. While CT and AVS were performed just as often within the 4 regions, a confirmatory test was performed in only 27% of patients within the US which is lower compared to EU and AU. Furthermore, due to geographic distances within the US the period of follow-up was frequently shorter. Although we found no significant differences in resolution rates between patients that did or did not undergo confirmatory testing and between the different follow-up periods, we cannot exclude that this has influenced the outcomes.

Similar to most studies regarding PA, the need for a retrospective design, due to the low prevalence of PA, is one of the weaknesses of our study. This made it impossible to use standardized measurement procedures for clinical outcomes such as blood pressure measurements. Although the duration of follow-up had no significant influence on resolution of hypertension rates, the short period of follow-up in a substantial number of patients could also be a potential weakness of this study. Also, the limited number of participating medical centers from CA and AU, resulting in relatively wide confidence intervals of the AUC, should be taken in to account.

As presented in earlier studies, the distribution of resolution rates might differ across countries or continents, which also was the case in our study[13-16]. In line, predictors for a certain outcome might differ between geographic populations and the effect or magnitude of predictors might change over time. Although dichotomous variables, as used within the ARS, simplify the use of prediction models in daily clinical practice, much information within the data is lost. This

was best illustrated by the significant higher mean BMI within the US, compared to the other 3 geographic regions, which did not lead to fewer patients with BMI ≤ 25 kg/m^2 and a lower ARS. Moreover, the cut-offs for dichotomized variables are often driven by the data, hampering the generalizability of prediction models[20-22]. Therefore, in future studies, a prediction model ideally should include continuous instead of dichotomous variables. Moreover, in a world of rising technology and easy access to electronic devices and web-based applications, a prediction model containing continues variables could be user friendly as well.

Conclusion

The ARS is a user-friendly prediction model for clinicians during patient counseling with a moderate to good predictive performance within current clinical practice. The model showed the highest predictive performance within North America, but potentially has less predictive performance in EU and AU indicating the potential limited generalizability outside of the North American APA population.

SUPPLEMENT 1 BIOCHEMICAL OUTCOMES AFTER UNILATERAL ADRENALECTOMY FOR PA

Variable	**All patients (n=435)**	**United States (n=248) (57%)**	**Europe (n=106) (24%)**	**Canada (n=42) (10%)**	**Australia (n=39) (9%)**	**Overall p-value**
	Number (%)	*Number (%)*	*Number (%)*	*Number (%)*	*Number (%)*	
Potassium level						
Measurement performed	415 (95%)	236 (95%)	105 (99%)	37 (88%)	37 (95%)	**0.038**
Hypokalemia	51 (12%)	46 (19%)	2 (2%)	1 (3%)	2 (5%)	**<0.001**
Aldosterone level						
Measurement performed	268 (62%)	175 (71%)	46 (43%)	21(50%)	26 (67%)	**<0.001**
Hyperaldosteronism	5 (2%)	3 (2%)	2 (4%)	0 (0%)	0 (0%)	0.482
Renin level/activity						
Measurement performed	157 (36%)	83 (34%)	38 (36%)	12 (29%)	24 (62%)	**0.005**
Suppressed	31 (20%)	26 (31%)	2 (5%)	2 (17%)	1 (4%)	**0.001**
ARR						
Measurement performed	156 (36%)	82 (33%)	38 (36%)	12 (29%)	24 (62%)	**0.005**
Elevated/Indicating PA	28 (18%)	14 (17%)	3 (8%)	6 (50%)	5 (21%)	**0.011**

Abbreviations: ARR = Aldosterone-to-Renin-Ratio; PA = Primary Aldosteronism.

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CHAPTER

7

General discussion & future directions

In this thesis we focused on the surgical treatment of primary aldosteronism (PA) in daily clinical practice. The two main goals described in this thesis were: (1) To give better insight in the performed preoperative work-up to surgery in daily clinical practice and (2) To describe the outcomes after surgery in terms of improvement of blood pressure control and decrease in antihypertensive drug burden. This general discussion will further elaborate on the main findings, clinical implications and future perspectives.

Preoperative work-up

In hypertensive patients, the work-up for PA mainly consists of two phases: (1) Screening for the disease followed by confirming the diagnosis and (2) Subtype testing to distinguish unilateral aldosterone-producing-adenoma (APA) from bilateral adrenal hyperplasia (BAH) to determine if patients should be treated with surgically or medically[1].

In hypertensive patients, the aldosterone-to-renin ratio (ARR) is widely used and the recommended screening modality for PA by the current Endocrine Society Guideline[1]. The ARR is based on a single blood sample and therefore seems to be a simple measurement. Though, in reality this is more complicated because of multiple interfering factors. For instance, serum potassium levels, the patients posture when the blood sample is taken and several medications are known to interfere with the test outcomes. Therefore, these factors should be accounted for, for instance by performing an adequate medication stop prior to testing, as recommended by the guideline[2-5]. Nevertheless, a lack of properly addressing these interfering factors in earlier studies is one of the reasons why the current guideline indicates that valid estimations of the diagnostic accuracy are lacking[1,2,6-12]. On this basis, we hypothesized that screening for the disease with only the ARR is not without a risk of missing a PA diagnosis. This may lead to unnecessary morbidity to these patients due to (lifelong) inadequate treatment of hypertension and the persisting aldosterone excess. In **chapter 2** we therefore aimed to evaluate the clinical consequences of screening with the ARR by assessing the diagnostic accuracy in a prospective study. In this study, a standardized ARR screening protocol was used, which was in line with the guideline. In addition, a confirmatory test was performed in all patients, regardless of ARR outcomes, as reference standard of the PA diagnosis. The results displayed a 100% sensitivity and 100% negative predictive value of the ARR in screening for PA. Therefore, we can presume that we can rely on the ARR as a screening test when performed under the standardized conditions as stated in the guideline. However, a substantial number of medical centers worldwide do not use a standardized sampling protocol as proposed by the guideline. Moreover, the laboratory assays used to measure the ARR could be of influence on the ARR outcome because they frequently differ between the medical centers. Consequently, in current clinical practice, patients are still falsely diagnosed as having PA and in others the diagnosis is not established. Furthermore, results showed a 87% specificity and 36% positive predictive value of the ARR. This indicates the need to perform a confirmatory test in case of a positive ARR, to rule out false positive ARR measurements, before establishing the PA diagnosis.

After confirming the PA diagnosis, subtype testing is essential to distinguish a unilateral APA from BAH[1]. Adrenal venous sampling (AVS) is recommended by the guideline for subtype testing[1]. Nevertheless, numerous controversies exist in literature regarding AVS. Therefore, the need to perform AVS in all, no or a selected group of patients is currently the main topic of discussion between experts in the field of PA[13-16]. **Chapter 3** gives insight in how the work-up to surgery was performed over the last years in multiple centers across the world. The results showed a large variability in work-up strategies used, indicating that clinicians frequently deviate from the guideline in daily clinical practice. This variability was not only present between the medical centers, but also between patients treated within each center. During the inclusion period of this study, the 2008 Endocrine Society Guideline was applicable[17]. In contrast to this guideline, confirmatory testing and AVS were performed in only one third and two third of the operated patients, respectively. This illustrates that clinicians most likely chose a specific work-up strategy based on their preferences or guided by case specifics. For instance, when we investigated the use of AVS, our results showed that almost all patients with bilateral disease or normal adrenal anatomy on computed tomography (CT) underwent AVS. Likewise, patients with a clear unilateral nodule on CT were less likely to undergo AVS, especially in case of larger tumors. The recommendation to perform AVS in all patients was changed within the new 2016 Endocrine Society Guideline. Nowadays, in case of age < 35 years old, hypokalemia, marked aldosterone excess and a clear unilateral adenoma on CT, AVS may not be needed any more. However, it should be taken into account that this recommendation was based on the lowest level of evidence[1]. In addition, within our study cohort only 6% of patients fulfilled these criteria and therefore this revision in the 2016 guideline has only marginal influence on clinical practice. We believe that this thesis illustrates the lack of uniform preoperative work-up worldwide, which is caused by the many disagreements in literature and between experts in the field of PA.

Benefits of surgery

In the past, many studies focused on describing complete clinical success, also named cure of hypertension, after surgery for PA (i.e., a normotensive patient without the need of antihypertensive medications). However, patients without complete clinical success may also benefit from surgery through a reduction of blood pressure and/or antihypertensive medications resulting in a subsequent decrease in morbidity, mortality and drug burden. Nonetheless, data on the precise decrease in blood pressure and antihypertensive medications is scarce in current literature[14,18-20]. **Chapter 4** focused on addressing this gap in literature. Although complete clinical success was present in only 27% of patients, 90% of patients showed any decrease in blood pressure and/or antihypertensive medications. Moreover, 58% of patients became normotensive on less or equal antihypertensive medications. Within these 58% of patients, the mean decrease in systolic blood pressure (SBP) exceeded 20 mmHg with a subsequent median decrease in defined daily dose (DDD) of 2, respectively. Most importantly, this study also showed a decrease in SBP of ≥ 10 mmHg in 41% of the patients with persistent hypertension after surgery (without an increase in antihypertensive medications). Therefore, these patients most likely benefitted from surgery as well, since research in hypertensive

patients showed a risk-reduction of 20% in cardiovascular morbidity and 13% in all-cause mortality for every 10 mmHg decrease in SBP[21,22]. Thereby, this thesis underlines the need to not only focus on complete clinical success but also on clinically relevant reduction in blood pressure and antihypertensive medications.

In 2017, the Primary Aldosteronism Surgical Outcome (PASO) Study Group introduced consensus criteria on outcomes after surgery for PA[14]. Within this consensus, based on the Delphi method, they were the first to establish standardized criteria for blood pressure related outcomes. By creating definitions for partial and absent clinical success they gave insight in the clinically relevant reduction in blood pressure and or antihypertensive medications. In **chapter 5** we evaluated the applicability of these PASO consensus criteria in daily clinical practice. Complete, partial and absent clinical success were achieved in 30%, 48% and 22%, respectively. This implies that in 78% of patients, surgery resulted in clear improvement of blood pressure control, but in 22% this was not the case. Further case by case evaluation of the PASO criteria revealed that in 11% of patients with partial clinical success and 47% of patients with absent clinical success, this classification could be doubted. This corresponded to 16% of the complete cohort. Therefore, multiple patients were most likely classified incorrectly as absent success instead of partial success and vice versa. As hypothesized, this was mainly due to the relatively high cut-off used to indicate a clinically relevant change in systolic blood pressure (i.e., ≥ 20 vs. ≥ 10 mmHg) and the use of percentages instead of absolute values to implicate a change in antihypertensive medications. For example, a patient with 15 mmHg reduction in SBP and 31% reduction in DDD was classified as absent success. However, the reduction in SBP by itself could be considered clinically relevant and moreover the absolute reduction in DDD was 2.7. To our opinion, this clearly shows partial clinical success indicating a pitfall of the PASO criteria in its current form.

Furthermore, cases with opposing change in blood pressure and antihypertensive medications remain challenging, especially because the relation between change in blood pressure and change in antihypertensive medications is complex. For instance, should a patient with 20 mmHg decrease in SBP and 1.5 DDD increase in antihypertensive medications be stratified as having partial or absent clinical success? In this thesis we were not able to give an answer to this question.

As presented within **chapter 4 and 5**, complete cure of hypertension after surgery for PA is no certainty. This stresses the importance of adequate patient counseling before performing an operation. The Aldosteronoma Resolution Score (ARS) is a model which could be used to predict the chance of complete clinical success after the operation[23]. Validation of the model in current daily clinical practice within a worldwide cohort was presented in **chapter 6**. Our results showed an area under the curve of 0.751 within the complete cohort. Furthermore, the model showed a negative predictive value of 93% in case of the lowest ARS and a positive predictive of 84% when a patient had the maximum ARS. We considered this diagnostic value as moderate to good, especially when we took into account that the ARS is such an easy to

use model only including 4 dichotomous variables (number of antihypertensive medications, body mass index, duration of hypertension and gender) [23]. Nevertheless, geographic validation of the ARS showed better prognostic performance within the United States and Canada compared to Europe and Australia. This potentially indicates a limited generalizability of the ARS outside North America and therefore the ARS could be less suited for the Dutch population. In the beginning of 2019, a new and promising prediction model was published by the PASO Study Group[24]. This model includes 6 pre-surgical variables: duration of hypertension, sex, body mass index, DDD, target organ damage and tumor size on imaging. They presented an area under the curve of 0.839 within their study cohort mainly consisting of European patients. Therefore this could be a potential alternative for the ARS. Nevertheless, this model has not been externally validated yet.

FUTURE DIRECTIONS

This thesis shows that the majority of patients with PA significantly benefits from surgery. However, the results also demonstrated a substantial number of patients without clear benefits. This raises the question: *''How can we further improve the benefits/outcomes of surgery in patients with PA?''*.

In multiple other surgically treatable diseases, outcomes were improved by enhancement of surgical techniques. In PA, however, we do not believe this is the case. There are multiple explanations for persistent hypertension after the operation. For instance, a patient with APA could simultaneously also have had primary hypertension and is this case there was a clear reason for surgery. However, other reasons could be a patient with BAH instead of APA or a patient with only primary hypertension and no PA at all. In these cases there actually was no indication for surgery, however, these patients underwent surgery because they were wrongly diagnosed. Therefore, to our opinion, the key to improve outcomes lies in correctly differentiating between primary hypertension and PA, followed by accurately distinguishing APA from BAH before performing surgery. A good work-up is essential to accurately diagnose patients and subsequently treat them accordingly. However, do we know what the best work-up is?

This thesis showed that the ARR is a perfect screening tool when performed under the standardized conditions as recommended by the guideline **(chapter 2)**. However, a substantial number of medical centers worldwide do not use a standardized sampling protocol. Therefore, we most likely still fail to diagnose the disease in a substantial group of patients due to false negative ARR results. Moreover, this thesis also showed that confirming tests are not routinely performed **(chapter 3)**. Therefore, we still could falsely diagnose patients as having PA because the ARR is not without false positive results **(chapter 2)**. Likewise, the discussion about whether AVS is crucial for adequate subtype testing has not been resolved. This illustrates that current literature is inconclusive and evidence is not compelling enough. Therefore, future studies should be performed to generate convincing evidence on the best work-up in PA.

To achieve this, accurate preoperative and postoperative registration of both biochemical and clinical (i.e., blood pressure related) outcomes is essential. However, the results in this thesis showed that in current daily practice the work-up is frequently performed at another institution and that many patients are lost to follow-up after the operation due to referral patterns **(chapters 3 – 6)**. We believe that further centralization of the work-up, treatment and follow-up to dedicated medical centers is the solution, as is also the case in other relatively rare diseases. This will enable these centers to incorporate a standardized work-up, treatment and follow-up regime in daily clinical practice and to prospectively collect data of all treated patients. As a result, unselected study populations will arise and through structural (international) collaborations it will be possible to properly compare outcomes and, above all, potential prognostic and influencing factors such as disease characteristics and work-up strategies. We believe this change is needed if we want to improve the benefits of surgery.

Furthermore, we hope that this thesis could inspire experts in the field of PA to further optimize and standardize the assessment of the blood pressure related outcomes. This is essential because only after establishing clear and valid outcome definitions, it is possible to properly investigate the best work-up strategy and the true prognostic and discriminating factors which could be used for patient counseling. Hopefully these future directions will help to answer the following research questions in the near future:

- Is it necessary to perform a confirmatory test in all patients?
- Do we need to perform AVS in all patients or is it safe to distinguish APA from BAH based on CT alone in a subgroup of patients?
- At what time after surgery (e.g. 3, 6 or 12 months) should the blood pressure related outcomes be assessed and how do these outcomes change over time?
- Which patients are less likely to achieve benefits of adrenalectomy and therefore potentially should not undergo surgery?

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APPENDICES

DUTCH SUMMARY/NEDERLANDSE SAMENVATTING

Hypertensie

Hypertensie, ook bekend als hoge bloeddruk, zorgt voor een verhoogde druk op de vaatwand en is gedefinieerd als een bloeddruk ≥140/90 mmHg[1-3]. Wereldwijd lijden 1.1 miljard mensen aan hypertensie wat gelijk staat aan 22% van de wereldwijde volwassen populatie[4,5]. Omdat meer dan 10 miljoen mensen per jaar sterven aan de gevolgen van hypertensie wordt de ziekte gezien als een serieus gezondheidsprobleem door de Wereldgezondheidorganisatie[6]. Buiten mortaliteit, zorgt hypertensie ook voor een verhoogde morbiditeit via bijvoorbeeld ziekten van het hart, de nieren of de hersenen. Omdat hypertensie vaak geen klachten veroorzaakt lopen veel mensen rond met een te hoge bloeddruk zonder dat dit wordt opgemerkt en behandeld. Het merendeel van de patiënten heeft primaire hypertensie, ook wel essentiële hypertensie genoemd. Primaire hypertensie heeft geen duidelijke lichamelijke oorzaak en wordt veelal veroorzaakt door gedragsfactoren zoals een slecht dieet, roken of te weinig lichamelijke beweging. Derhalve kan dit ook niet worden behandeld met een operatie. Secondaire hypertensie wordt daarentegen veroorzaakt door onderliggende lichamelijke ziektes van nieren, bloedvaten, hart of de hormoonproducerende organen.

Primair hyperaldosteronisme

Primair hyperaldosteronisme (PA), is de meest voorkomende vorm van secondaire hypertensie. Momenteel wordt geschat dat in circa 5% van de patiënten met hypertensie, dit wordt veroorzaakt door PA[7-10]. Aangezien 22% van de wereldwijde volwassen populatie hypertensie heeft zou dit betekenen dat circa 1 op de 100 volwassenen lijdt aan PA[11,12]. PA wordt veroorzaakt door een te hoge productie van het hormoon aldosteron door een of beide bijnieren[13]. Dit overschot aan aldosteron zorgt voor een te hoge opname van zout en vocht in de nieren met een hoge bloeddruk als gevolg. Naast hypertensie is ook het hyperaldosteronisme een onafhankelijke oorzaak van morbiditeit en mortaliteit. Dit komt doordat de hoge aldosteron gehaltes in het bloed zorgen voor bijvoorbeeld verlittekening in de vaten, de nieren of het hart. Hierdoor draagt PA bij aan ziektes zoals nierfalen, hartfalen en een herseninfarct[12,14-16]. De klassieke presentatie van een patiënt met PA is een persoon met therapieresistente hypertensie, gedefinieerd als een persisterend verhoogde bloeddruk ondanks 3 of meer antihypertensiva, en hypokaliaemie, dat wordt veroorzaakt door verhoogde uitscheiding van kalium in de nieren[13].

De chirurgische behandeling van primair hyperaldosteronisme

PA wordt voornamelijk veroorzaakt door een aldosteron-producerend-adenoom (APA)(35 – 40%) of door bilaterale hyperplasie (60 – 65%)[11,13,17]. Omdat bij een APA slechts één van beide bijnieren is aangedaan wordt dit bij voorkeur behandeld door een unilaterale adrenalectomie, het chirurgisch verwijderen van één van beide bijnieren. Bij bilaterale hyperplasie zijn beide bijnieren aangedaan. Omdat de bijnieren naast aldosteron nog meer hormonen produceren zou het verwijderen van beide bijnieren leiden tot een levenslang hormoon tekort. Derhalve wordt bilaterale hyperplasie medicamenteus behandeld met aldosteron remmers[11]. De

adrenalectomie vindt plaatst via een minimaal invasieve kijkoperatie waardoor de operatie relatief weinig complicaties heeft en patiënten vaak enkele dagen na de operatie weer met ontslag kunnen[18-20].

Doel van dit proefschrift

In de huidige literatuur is onvoldoende bekend over hoe we momenteel de work-up naar chirurgie uitvoeren en wat het precieze effect is van een operatie op de bloeddruk. Daarom wordt in dit proefschrift gefocust op preoperatieve work-up en de resultaten van de chirurgische behandeling van PA in de hedendaagse praktijk.

Preoperatieve work-up

De huidige richtlijn adviseert om patiënten met hypertensie te screenen op PA door gebruik te maken van de aldosteron-renine-ratio (ARR). Dit is een bloedtest waarbinnen verschillende hormonen met elkaar worden vergeleken. Hoewel deze test momenteel wordt aanbevolen is er in de huidige literatuur onvoldoende bekend over de diagnostische accuratesse van de ARR[11]. Indien de ARR een niet voldoende betrouwbare screenende test is, zou dit betekenen dat patiënten onnodig behandeling van de ziekte mislopen met alle risico's van dien. Derhalve hebben wij de diagnostische accuratesse van de ARR onderzocht in een gestandaardiseerd en prospectief onderzoek. De resultaten hiervan zijn beschreven in **hoofdstuk 2**.

Na screening middels de ARR moet een extra diagnostische test (confirmatory test) worden uitgevoerd om een vals positieve ARR uit te sluiten en daarmee de diagnose te bevestigen[11]. Wanneer de diagnose met een confirmatory test is bevestigd wordt een computed tomography (CT) scan verricht om zeldzame vormen van bijnierkanker uit te sluiten en om de eerste stap te zetten in het maken van onderscheid tussen het chirurgische te behandelen eenzijdige APA en de medicamenteus te behandelen bilaterale hyperplasie. De huidige richtlijn adviseert echter om het definitieve onderscheidt te baseren op Adrenal Venous Sampling (AVS), een dure en lastige techniek die niet in alle ziekenhuizen beschikbaar is[11]. In de huidige literatuur en tussen experts op het gebied van PA is er dan ook veel controverse omtrent de preoperatieve work-up. Hierbij vraagt men zich hardop af welke stappen en diagnostische testen noodzakelijk zijn voor het accuraat behandelen van PA. Potentieel leidt dit tot een grote diversiteit in preoperatieve work-up in de hedendaagse praktijk, echter is dit in de huidige literatuur niet beschreven. Derhalve hebben wij in **hoofdstuk 3** onderzocht hoe verschillende ziekenhuizen wereldwijd de preoperatieve work-up hebben uitgevoerd.

Resultaten van de operatie

Omdat zowel hypertensie als hyperaldosteronisme bijdragen aan morbiditeit en mortaliteit is het ultieme doel van de operatie het volledig genezen van beide. Genezing van hyperaldosteronisme wordt beschreven in het grootste deel van de patiënten[21-23]. Complete genezing van de hypertensie daarentegen is verre van een zekerheid met een geschat genezingspercentage van ≤ 50%. Echter ook patiënten zonder complete genezing van hypertensie kunnen baat hebben bij een operatie doordat zij potentieel reductie van bloeddruk

en/of antihypertensiva hebben wat zorgt voor afname van morbiditeit, mortaliteit en medicamenteuze bijwerkingen. Zeker omdat bekend dat is dat iedere 10 mmHg daling in systolische (boven) bloeddruk resulteert in 20% afname in morbiditeit en 13% afname in mortaliteit[24,25]. In het verleden zijn meerdere studies uitgevoerd die het percentage patiënten met volledige genezing van hypertensie beschrijven, echter is er weinig data omtrent de precieze afname in bloeddruk en medicatie naar de operatie. Daarom beschrijven wij in **hoofdstuk 4** de exacte reductie in bloeddruk en antihypertensiva na chirurgie voor PA.

De Primary Aldosteronism Surgical Outcome (PASO) studiegroep was in 2017 de eerste die specifieke consensus criteria publiceerde met het doel het gestandaardiseerd beschrijven van de reductie in bloeddruk en antihypertensiva na een operatie[21]. Zij hanteerde 3 definities: Volledig, gedeeltelijk en geen klinisch succes. Patiënten met volledig klinisch succes waren genezen van de hypertensie en hadden een normale bloeddruk zonder gebruik van antihypertensiva. Patiënten met gedeeltelijk succes waren niet geheel genezen maar hadden wel evident baat bij de operatie door een afname in systolische bloeddruk ≥ 20 mmHg en/of een afname van ≥ 50% in antihypertensiva. Alle andere patiënten waren gedefinieerd als geen klinisch succes wat impliceert dat zij geen of onvoldoende baat bij de operatie hebben gehad[21]. Naar onze mening was de grenswaarde die werd gebruikt om een relevante daling in bloeddruk te beschrijven te hoog, namelijk ≥ 20 i.p.v. ≥ 10 mmHg. Tevens vonden wij het gebruik van een percentage in plaats van een absolute waarde om reductie in antihypertensiva aan te duiden risicovol. Een daling van 4 naar 2 antihypertensiva of van 2 naar 1 antihypertensivum is namelijk beide 50% echter is de absolute daling wezenlijk verschillend. Onze hypothese was dat de PASO criteria patiënten onterecht zou classificeren als geen klinisch succes in plaats van gedeeltelijk succes en vice versa. Zodoende hebben wij het gebruik van deze PASO criteria in de hedendaagse praktijk geanalyseerd in **hoofdstuk 5**.

Zoals eerder genoemd is volledige genezing van hypertensie na een operatie verre van een zekerheid. Derhalve is het goed preoperatieve inlichten van patiënten en het managen van hun verwachtingen essentieel. De Aldosteronoma Resolution Score (ARS) is een predictiemodel dat door artsen gebruikt kan worden om de kans op volledige genezing in te schatten[26]. Het model is voor artsen makkelijk te gebruiken in de spreekkamer en bevat enkel 4 variabelen: geslacht, gewicht, aantal jaar hypertensie en aantal antihypertensiva[26]. Het model is echter 10 jaar geleden ontwikkeld en gebaseerd op de Amerikaanse populatie. Omdat bekend is dat de voorspellende waarde van een predictiemodel kan veranderen met de tijd en tevens kan afwijken bij toepassing op andere populaties hebben wij de voorspellende waarde van de ARS onderzocht in de hedendaagse tijd binnen ons internationale cohort. De resultaten van dit onderzoek zijn beschreven in **hoofdstuk 6**.

Internationale CONNsortium studiegroep

De internationale CONNsortium studiegroep is een samenwerkingsverband tussen 16 medische centra vanuit de Verenigde Staten, Canada, Australië en Europa en is in 2016 opgezet vanuit het Universitair Medisch Centrum Utrecht. Data van alle geopereerde patiënten tussen 2010

– 2016 is retrospectief verzameld en gezamenlijk vormt dit de basis voor de **hoofdstukken 3 – 6** van dit proefschrift. Momenteel is de internationale CONNsortium studiegroep, naast de PASO studiegroep, toonaangevend in het huidige onderzoek naar PA.

Onderzoeksdoelen per hoofdstuk
Hoofdstuk 2: Het bestuderen van de diagnostische accuratesse van de ARR door gebruik te maken van een gestandaardiseerd en prospectief studieprotocol wat gebaseerd is op de huidige richtlijnen.
Hoofdstuk 3: Het onderzoeken van de verschillende preoperatieve work-up strategieën die in de hedendaagse praktijk wereldwijd worden gebruikt.
Hoofdstuk 4: Het exact beschrijven van de reductie in bloeddruk en antihypertensiva na adrenalectomie om zodoende de baat die patiënten hebben bij chirurgie voor PA beter inzichtelijk te maken.
Hoofdstuk 5: Het evalueren van de PASO consensus criteria voor klinisch succes na chirurgie voor PA.
Hoofdstuk 6: Het valideren van de ARS binnen de huidige populatie van patiënten met PA.

BEVINDINGEN IN DIT PROEFSCHRIFT EN DISCUSSIE

Dit proefschrift is gericht op de chirurgische behandeling van PA in de hedendaagse praktijk. Er waren twee hoofddoelen: (1) Het verkrijgen van beter inzicht in de preoperatieve work-up die wereldwijd wordt gebruikt en (2) Het onderzoeken en accuraat beschrijven van de afname in bloeddruk en antihypertensiva om zodoende meer inzicht te krijgen in de baat die patiënten hebben bij een operatie.

Preoperatieve work-up
In hypertensieve patiënten bestaat de work-up voor PA eigenlijk uit 2 fases: (1) Screening naar de ziekte gevolgd door het bevestigen van de diagnose middels een extra test en (2) Het onderscheiden van het unilaterale APA van bilaterale hyperplasie om zodoende te beoordelen of patiënten middels chirurgie of medicamenteus behandeld moeten worden[11].

Voor screening wordt vanuit de huidige richtlijn geadviseerd om gebruik te maken van de ARR[11]. De ARR is gebaseerd op slechts één bloedafname en daarom lijkt dit een simpele test om uit te voeren. In de realiteit is deze test echter meer complex aangezien er meerdere factoren bekend zijn die de testuitslag kunnen beïnvloeden. De beste voorbeelden hiervan zijn de hoogte van het kalium en een groot scala aan, voornamelijk bloeddruk verlagende, medicijnen[11,27-30]. De richtlijn adviseert dan ook om deze factoren onder controle te houden door bijvoorbeeld het corrigeren van een te laag kalium gehalte en door de betreffende medicatie meerdere weken voorafgaand aan de meting reeds te staken. De eerder uitgevoerde studies naar de diagnostische waarde van de ARR hebben echter niet al deze factoren adequaat ondervangen en derhalve kan men de betrouwbaarheid van de ARR in twijfel trekken.

Zodoende hebben wij in **hoofdstuk 2** een prospectieve studie gedaan naar de diagnostische waarde van de ARR waarbij een gestandaardiseerd studieprotocol is gebruikt dat was gebaseerd op de huidige richtlijn. De resultaten toonden een 100% sensitiviteit en 100% negatief voorspellende waarde. Dit betekent dat de ARR een ideale screenende test is mits hij wordt uitgevoerd zoals geadviseerd in de richtlijn. Echter worden deze adviezen wereldwijd niet in alle centra opgevolgd en derhalve is er nog steeds het risico dat de diagnose bij patiënten wordt gemist. De resultaten toonden verder een 87% specificiteit en 36% positief voorspellende waarde wat betekent dat de extra test (confirmatory test) noodzakelijk blijft om de diagnose definitief te bevestigen. Dit kan echter als normaal worden beschouwd voor een screenende test.

Nadat de diagnose PA is bevestigd is het essentieel om onderscheid te maken tussen APA en bilaterale hyperplasie. In de huidige richtlijn wordt AVS hiervoor als het beste diagnosticum beschreven. Desalniettemin is de huidige literatuur niet eenduidig omtrent de meerwaarde van AVS. Dit maakt de noodzaak om AVS uit te voeren in alle, of slechts een subgroep van patiënten, een van de belangrijkste gespreksonderwerpen tussen experts op het gebied van PA[31-34]. Binnen deze discussie zijn er duidelijke voor- en tegenstanders van AVS. **Hoofdstuk 3** geeft ons beter inzicht in hoe de preoperatieve work-up momenteel wereldwijd wordt uitgevoerd. De resultaten tonen een grote variabiliteit in work-up wat aanduidt dat dokters frequent afwijken van de richtlijn in de dagelijkse praktijk. Deze verschillen werden zowel tussen de centra, als binnen een centrum zelf waargenomen. AVS werd in slechts 2/3^{e} van de patiënten uitgevoerd wat betekent dat de dokter de noodzaak voor AVS beoordeelde per casus. Veelal kwam dit doordat deze patiënten op CT een duidelijke afwijking hadden in één van beide bijnieren waarna de behandelend specialist besloot dat AVS niet geïndiceerd was omdat deze karakteristieken op CT als typisch passend bij APA werden beoordeeld. Naar onze mening illustreert dit proefschrift het gebrek aan uniformiteit betreffende de preoperatieve work-up, dat wordt veroorzaakt door het gebrek aan bewijs in de huidige literatuur.

Resultaten van de operatie

De mate van reductie in bloeddruk en antihypertensiva na een operatie voor PA is zeer relevant omdat dit leidt tot reductie van morbiditeit, mortaliteit en medicamenteuze bijwerkingen. Desondanks is dit in de huidige literatuur niet voldoende beschreven[21-23,35]. Derhalve hebben wij ons in **hoofdstuk 4** gericht op het vullen van deze lacune in de huidige literatuur. Ondanks dat de resultaten slechts complete genezing van hypertensie toonden in 27% van de patiënten had wel 90% van de patiënten een afname van bloeddruk en/of antihypertensiva. Tevens had 58% van de patiënten een daling van de bloeddruk <140/90 mmHg na de operatie, hoewel een deel hier nog wel antihypertensiva bij nodig had. Binnen deze 58% van de patiënten werd een mediane systolische bloeddruk daling gezien boven de 20 mmHg met ook een duidelijke afname in antihypertensiva. Daarnaast had ook 41% van de patiënten met een bloeddruk ≥140/90 mmHg na de operatie toch een systolische bloeddruk daling ≥ 10 mmHg. Hierdoor hebben ook deze patiënten waarschijnlijk baat gehad bij de operatie aangezien bekend is dat dit leidt tot 20% reductie in morbiditeit en 13% in mortaliteit[24,25]. Dit proefschrift toont de

noodzaak om niet enkel te focussen op volledige genezing van hypertensie maar ook op klinisch relevante reductie van bloeddruk en antihypertensiva na de operatie.

Zoals eerder was de PASO studiegroep de eerste die duidelijke definities introduceerde om de afname in bloeddruk en antihypertensiva te categoriseren[21]. Vooral met hun definities van gedeeltelijk en geen klinisch succes brachten zij een toevoeging aan de eerdere literatuur. In **hoofdstuk 5** hebben wij het gebruik van deze definities getest in een internationaal cohort wat representatief is voor de huidige klinische praktijk. De resultaten toonden volledig, gedeeltelijk en geen klinisch succes in respectievelijk 30%, 48% en 22% van de patiënten. Dit impliceert dat 78% van de patiënten duidelijk baat bij de operatie hadden door reductie in bloeddruk en/of antihypertensiva, echter zou 22% ook geen evidente baat hebben gehad bij de operatie. Vervolgens hebben wij dit per patiënt geëvalueerd waarbij wij in 11% van de patiënten met gedeeltelijk klinisch succes en 47% van de patiënten met geen klinisch succes het niet eens waren met deze classificatie of eraan twijfelden. Naar onze mening waren deze patiënten onterecht gecategoriseerd als geen in plaats van gedeeltelijk klinisch succes en vice versa. Dit was voornamelijk gebaseerd op het te hoge afkappunt dat werd gebruikt om een relevante daling in systolische bloeddruk te duiden, ≥ 20 i.p.v. ≥ 10 mmHg, en het gebruik van een percentage in plaats van een absolute waarde om afname in antihypertensiva te duiden. Een patiënt met 15 mmHg daling in systolische bloeddruk en 31% afname in antihypertensiva werd bijvoorbeeld als geen klinisch succes geclassificeerd. Naar onze mening is deze daling in bloeddruk reeds voldoende om dit als gedeeltelijk klinisch succes in te delen, daarbij was de absolute daling van antihypertensiva in deze patiënt meer dan 2 wat onze theorie nog meer ondersteund heeft. Ondanks dat de PASO studiegroep met de introductie van deze criteria een grote stap voorwaarts heeft gezet richting het gestandaardiseerd beoordelen van bloeddruk gerelateerde uitkomsten, toont dit proefschrift de potentiele fouten en beperkingen van de huidige criteria.

Zoals is getoond in **hoofdstuk 4 en 5** is complete genezing van hypertensie na de operatie verre vanzeker. Dit wijst nogmaals op de noodzaak om voor de operatie patiënten adequaat voor te lichten zodat zij met de juiste verwachtingen een operatie ondergaan. De ARS is een predictiemodel dat gemakkelijk gebruikt kan worden door dokters in de spreekkamer[26]. Het model is echter meer dan 10 jaar geleden ontwikkeld wat maakt dat het lastig in te schatten is of het in de huidige praktijk nog betrouwbaar genoeg is. Derhalve hebben wij dit model in de hedendaagse praktijk gevalideerd binnen ons internationale cohort in **hoofdstuk 6**. De resultaten toonden een area under the curve (AUC) van 0.751 in het complete cohort. Tevens werd een negatieve voorspellende waarde van 93% aangetoond in het geval van de laagste ARS en een positief voorspellende waarde van 84% in het geval van de hoogste ARS. Naar onze mening toont dit aan dat de ARS een gemiddeld tot goed predictiemodel is om te gebruiken, zeker wanneer men in deze overweging meeneemt dat het een erg gemakkelijk te gebruiken model is. Verdere geografische validatie van het model toonde de hoogste voorspellende waarde binnen de Noord Amerikaanse populatie maar een lagere voorspellende waarde binnen de Europese en Australische subgroep van ons cohort. Hierdoor is de ARS mogelijk minder

geschikt om te gebruiken binnen Nederland. In het voorjaar van 2019 is een nieuw en meer complex predictiemodel vanuit de PASO studiegroep gepubliceerd dat potentieel goed te gebruiken kan zijn binnen Europa. Wereldwijde validatie moet dit echter nog gaan aantonen[36].

De toekomst

Dit proefschrift heeft aangetoond dat de meerderheid van de patiënten met PA significant baat heeft bij een operatie. Echter toonden de resultaten ook een groep patiënten zonder duidelijk profijt. Dit roept de vraag op: *''Hoe kunnen we de resultaten van een operatie bij patiënten met PA verder verbeteren?''*.

In verschillende andere chirurgisch te behandelen ziektes werden uitkomsten verbeterd via de ontwikkeling van nieuwe en betere operatietechnieken. Wij geloven echter niet dat dit voor PA ook geldt. Potentiele verklaringen voor persisterende hypertensie na de operatie zijn namelijk: (1) Een patiënt die is geopereerd eigenlijk bilaterale hyperplasie had in plaats van een APA, (2) Een patiënt die PA heeft echter daarnaast ook primaire hypertensie of (3) Een patiënt die enkel primaire hypertensie had een eigenlijk helemaal geen PA. Daarom is naar onze mening de sleutel tot het verbeteren van de uitkomsten het adequaat differentiëren tussen een patiënt met enkel primaire hypertensie en een patiënt met PA. Dat gevolgd wordt door het accuraat onderscheiden van APA en bilaterale hyperplasie alvorens wordt besloten of een operatie zinvol is. Concluderend is een adequate preoperatieve work-up essentieel. Echter weten we momenteel wel wat de beste work-up is?

Dit proefschrift toont dat de ARR een perfect middel voor screening is wanneer het wordt uitgevoerd zoals beschreven in de richtlijnen **(hoofdstuk 2)**. Wereldwijd wordt de ARR echter in verscheidene centra niet als dusdanig uitgevoerd waardoor we potentieel veel patiënten met PA niet diagnosticeren en behandelen. Tevens toont dit proefschrift dat een confirmatory test niet routinematig bij alle patiënten wordt uitgevoerd **(hoofdstuk 3)**. Dit leidt er waarschijnlijk toe dat op basis van een vals positieve ARR uitslag patiënten worden gediagnosticeerd met PA en mogelijk dus ook een operatie ondergaan terwijl zij daar waarschijnlijk geen baat bij hebben omdat zij enkel primaire hypertensie hebben. Daarnaast is de discussie omtrent de noodzaak om AVS uit te voeren in alle patiënten nog verre van opgelost. Bovenstaande wijst erop dat het bewijs in de huidige literatuur onvoldoende en niet overtuigend genoeg is om gezamenlijk de beste work-up strategie te kiezen en wereldwijd structureel uit te voeren. Daarom moet toekomstig onderzoek worden gedaan om overtuigend bewijs te leveren.

Om dit te bereiken is het essentieel om zowel voor als na de operatie de laboratorium uitslagen en de bloeddruk gerelateerde uitkomsten accuraat te controleren en registeren. In de hedendaagse praktijk daarentegen wordt de work-up en follow-up vaak uitgevoerd in andere centra dan waar de operatie heeft plaats gevonden doordat patiënten worden doorverwezen **(hoofdstuk 3 – 6)**. Net als bij andere relatief zeldzame ziektebeelden geloven wij erin dat verdere centralisatie van de work-up, behandeling en follow-up van PA naar enkele

gespecialiseerde ziekenhuizen de oplossing is. Dit maakt het voor deze ziekenhuizen namelijk mogelijk om een gestandaardiseerde manier van work-up, behandeling en follow-up te hanteren en prospectief alle data te registreren. Dit moet leiden tot hoge kwaliteit van data en via structurele (internationale) samenwerkingsverbanden moet het mogelijk worden om nauwkeurig uitkomsten met elkaar te vergelijken om vervolgens de beste work-up strategieën en prognostische factoren te selecteren.

Tevens hopen wij dat dit proefschrift experts op het gebied van PA kan inspireren om de beoordeling van de bloeddruk gerelateerde uitkomsten na een operatie verder te classificeren en standaardiseren. Het is namelijk essentieel om valide definities van de te behalen uitkomsten te hebben alvorens prognostische factoren adequaat kunnen worden onderzocht. Hopelijk kunnen we via deze weg in de nabije toekomst gezamenlijk de volgende vraagstukken beantwoorden:

- Is het noodzakelijk om een confirmatory test bij alle patiënten uit te voeren?
- Moeten we AVS bij alle patiënten uitvoeren of is het veilig om in een subgroep van patiënten APA te onderscheiden van bilaterale hyperplasie op basis van alleen CT?
- Hoe lang na een operatie is het mogelijk om de bloeddruk gerelateerde uitkomsten adequaat te beoordelen (bijv. 3, 6 of 12 maanden) en veranderen deze uitkomsten over de tijd?
- Welke patiënten hebben een lage kans om baat te hebben bij een operatie en moeten zij dan geen operatie ondergaan?

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Jaarclubgenoten, na geweldige jaren tijdens onze studententijd hebben we ook nu nog een hechte kern. Onze lustrumreis naar de Filipijnen en de jaarlijkse trip naar Don Paat in Barca zijn dingen om nooit te vergeten.

Renske en Veerle, mijn 2 grote zussen, we kunnen altijd bij elkaar terecht en we vertrouwen elkaar. Heel mooi dat we alle drie arts zijn geworden en dat jullie mijn paranimfen zijn! Ook wil ik jullie bedanken voor jullie bijdrage aan dit proefschrift. Zowel in het Antonius als het UMCU heb ik met jullie samen kunnen werken en dat blijft toch heel speciaal. Hopelijk hebben we in de toekomst een longarts, cardioloog en chirurg in het gezin en misschien werken we dan weer samen in hetzelfde ziekenhuis!

Lieve papa en mama, jullie hebben ons opgevoed met veel vrijheid en vertrouwen wat heeft geleid tot het fijne gezin wat we nu hebben. Er wordt altijd een situatie gecreëerd waarin wij

ons kunnen ontwikkelen, we zijn vrij om fouten te maken en jullie staan altijd achter ons. Jullie mogen trots zijn! Ik betwijfel of ik ooit terug kan doen wat jullie allemaal voor mij gedaan hebben.

Lieve Rio, schatje, al bijna 10 jaar heb ik het geluk om met jou samen te mogen zijn! Je bent mijn maatje en het beste wat mij ooit is overkomen. Iedere dag ben ik nog blij om met jou samen te zijn. Schatje, ik houd van jou!

CURRICULUM VITAE

Wessel Mathieu Corneel Marie Vorselaars was born on the 24th of May 1990 in Tilburg, as the son of Ad Vorselaars and Els Beurskens. He grew up with his older sisters Renske and Veerle. After graduating high school at the Theresia Lyceum in 2008 he relocated to Utrecht. At first, he studied Law and Psychology and in 2010 he was given the chance to study Medicine.

In his 4th year of medical school he started participating in scientific research at the Department of Endocrine Surgery under the supervision of Prof. dr. M.R. Vriens, Prof. dr. I.H.M. Borel Rinkes, Prof. dr. G.D. Valk and dr. W. Spiering. At first, he contributed to multiple separate research projects. During his last year of medical school he started his PhD program on the preoperative work-up and surgical treatment of primary aldosteronism in current daily practice. During this period he initiated a multicenter international collaboration, the International CONNsortium study group, which formed the basis of his PhD thesis.

After graduating from medical school in the winter of 2016 he started working as a surgical resident not in training at the St. Antonius Hospital under the supervision of dr. D. Boerma. Between January 2018 and June 2019 he gained clinical academic experience at the Department of Surgery of the University Medical Center Utrecht (Head Prof. dr. M.R. Vriens). Currently he is working as a surgical resident not in training at the Diakonessenhuis under the supervision of dr. T. van. Dalen. He combined these years of clinical work with research and finishing his PhD thesis. In 2018 and 2019 his research work has received awards at the 39th and 40th Annual Meeting of the American Association of Endocrine Surgeons.