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Review Article

Trends in blood pressure-related outcomes after adrenalectomy in patients with primary aldosteronism: A systematic review

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ABSTRACT

Background: Decrease in blood pressure (BP) is the major goal of adrenalectomy for primary aldosteronism. Nevertheless, the optimal timing to assess these outcomes and the needed duration of follow-up are uncertain. We systematically reviewed the literature regarding trends in BP-related outcomes during follow-up after adrenalectomy.
Methods: A systematic literature search of medical literature from PubMed, Embase and the Cochrane Library regarding BP-related outcomes (i.e. cure of hypertension rates, BP and antihypertensives) was performed. The Quality In Prognosis Studies risk of bias tool was used.
Results: Of the 2057 identified records, 13 articles met the inclusion criteria. Overall study quality was low. In multiple studies, the biggest decrease in BP was shown within the first month(s) after adrenalectomy and afterwards BP often remained stable during long-term follow-up.
Conclusions: Based on the available studies one might suggest that long follow-up is unnecessary, since outcomes seem to stabilize within the first months.

Introduction

Primary Aldosteronism (PA), first described by Jerome. W. Conn in 1955[1], is a typical form of secondary hypertension (HTN) with a prevalence of 5–13% among patients with HTN.[2] Bilateral hyperplasia is treated by medication, whereas unilateral aldosterone-producing-adenoma preferably is treated with adrenalectomy. The goal of surgery is to correct aldosteronism, lower blood pressure (BP) and decrease or stop antihypertensive medication (AHT). Biochemical cure rates, i.e. normalization of aldosteronism, range from 90 to 100% after surgery.[3–5] Nevertheless, clinical cure, i.e. normalization of BP (systolic <140 mmHg/diastolic <90 mmHg) without the use of AHT, are much lower with reported cure rates ranging from 27 to 37% within large, international multicenter studies.[5–7]

The Endocrine Society Guideline states that BP typically normalizes or shows maximum improvement between 1 and 6 months after surgery, but can continue to fall up to 1 year after surgery.[8] Similarly, the Primary Aldosteronism Surgical Outcome (PASO) study group recommends, based on a consensus among international experts, initial outcome assessment within the first 3 months after surgery and final outcome assessment between 6 and 12 months after surgery.[5] Nevertheless, both recommendations were not substantiated by literature. This may illustrate that the ideal timing of outcome assessment after surgery for PA is still uncertain. This is of importance because studies showed that it can be challenging to complete one-year follow-up after surgery in daily clinical practice, especially within medical centers with referral patterns covering large geographical distances.[6,7,9]

Therefore, the aim of this study was to systematically review the literature regarding trends in BP-related outcomes during follow-up with the goal to come to a meaningful advice regarding the duration of follow-up needed after surgery for PA.

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Material and methods

This systematic review is reported according to the Standard Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10]

Literature search strategy

The online electronic databases PubMed, Embase and Cochrane Library were consulted, and searched on the 1st of January 2020. A systematic search was performed using the following search terms and their synonyms: patients with PA AND unilateral adrenalectomy AND BP-related outcomes and follow-up (Supplementary 1). The search was limited to articles published after 1-1-1990 and only articles in English or Dutch were included. Duplicates were removed using Mendeley.[11] Two reviewers (DS and WV) independently conducted the screening of relevant titles and abstracts according to inclusion and exclusion criteria. Screening was performed using Rayyan.QCRI.[12] Full text of articles of interest were retrieved and screened for eligibility by two reviewers (DS and WV) independently. Cross referencing of systematic reviews found in the search for additional potentially relevant articles was performed.

Inclusion and exclusion criteria

The following inclusion criteria were applied: 1) patients underwent unilateral total adrenalectomy; and 2) postoperative BP or clinical cure rate were measured during at least two different follow-up moments. The first follow-up moment should be at or within 6 months after surgery. Studies were excluded in case of 1) no full text available; 2) case reports, letters, editorials or conference abstracts; 3) non-adult population (<18 years) or pregnant population and; 4) KCNJ5 mutation studies; and 5) if the language was not English or Dutch. In case articles reported data on the same patient cohort, the article best matching the inclusion criteria was selected.

Extraction of data

Data were extracted according to a standardized format in an Excel spreadsheet by an individual reviewer (DS). The following study characteristics were collected: first author, year of publication, country, city, study type, inclusion period, number of patients, preoperative work-up, pathology results and follow-up duration. Also, multiple BP-related parameters were collected if presented within the study: preoperative systolic BP (SBP) and diastolic BP (DBP) with AHT usage, postoperative SBP and DBP for each provided follow-up moment with AHT usage, and clinical cure rates with outcome definition.

Risk of bias assessment

The Quality In Prognosis Studies (QUIPS) tool was used to assess risk of bias.[13] The tool consists of six domains which were tailored to meet specific quality assurance for this systematic review (Supplementary 2). Each domain was given an outcome, which could be ‘high’, ‘moderate’ or ‘low’ risk of bias. Eventually, overall risk of bias of the studies was scored with ‘high’, ‘moderate’ or ‘low’ risk of bias, by taking into account the outcome of each domain, with special attention to the domains of ‘study participation’, ‘study attrition’, ‘prognostic factor measurement’ and ‘outcome measurement’. The following confounders were defined using the PASO study[5]: age, gender, BMI, preoperative SBP/DBP, duration of HTN and number of AHT.

Results

Literature search results

The total number of records identified through database searching was 2057, of which 497 duplicates were removed and 1494 articles were excluded after screening on titles and abstracts (Fig. 1). Sixty-six studies were included for full-text assessment. We excluded 48 studies based on the following reasons: only one postoperative BP or clinical cure rate reported (n = 47); same cohort (n = 1). Finally, 18 articles were thoroughly read and assessed for eligibility, of which five articles were excluded for the following reasons: only postoperative outcomes beyond 6 months (n = 1); PA subgroup results not reported (n = 1); only short-term BP and long-term clinical cure rate (n = 3). Eventually, 13 studies were included in this review.[14–26] Cross referencing did not yield any additional articles which could be included.

Study characteristics

The studies were published between 1992 and 2019, with patient inclusion ranging from 1975 to 2017 (Table 1 & Supplementary Table 1). The number of included patients ranged from 9 to 156; overall a total of 666 patients were included. Most of the studies (n = 9) were retrospective studies and four were prospective studies. The preoperative diagnostics and imaging techniques used during work-up differed between studies. Mean or median follow-up ranged from 6 to 138 months. A broad description of each individual study can be found in Supplementary 3.

Risk of bias assessment

Five studies had a moderate risk of bias[16,19–22] and six studies scored high risk of bias (Table 2).[14,15,17,23,24,26] Two studies had little concerns regarding bias for this review and were scored with low risk of bias.[18,25] Van der Linden et al. scored low risk of bias on all domains.[25] Citton et al. scored low risk of bias on all domains except for ‘prognostic factor measurement’ and ‘outcome measurement’.[18] Most studies scored high or moderate risk of bias on the domain ‘study participation’, because identifying methods and inclusion and exclusion criteria were often not clearly described. In addition, several studies retrospectively included patients based on completeness of data (i.e. patients with missing data were excluded), which led to none lost to follow-up and, therefore, doubtful scores of low risk of bias in the domain ‘study attrition’.[16,17,20,24–26] All but one study[25] showed moderate or high risk of bias concerning measurement of the prognostic factors and outcomes, which were poorly described. Moreover, the methods of BP measurements (e.g. type of measurement, patient positioning, used devices, multiple readings) were often lacking or poorly reported. Furthermore, most studies scored a high or moderate risk of bias on ‘study confounding’ because confounders were not defined, measured, or adjusted for.

Blood pressure follow-up and clinical cure rates

Eleven studies reported preoperative and postoperative SBP and/or DBP provided in means or medians,[14,16,18–26] one study used Mean Blood Pressure (MBP)[15] and one study only presented clinical cure rates (Table 3).[17] Ten studies provided first postoperative SBP and DBP measurements at or within one month after surgery.[14–16,18–20,22–25] Two studies reported first postoperative BP measurements at six months after surgery.[21,26] Eight studies reported SBP measurements at long-term follow-up (median 6–59 months).[16,18,19,21–23,25,26] Nine studies reported BP measurements

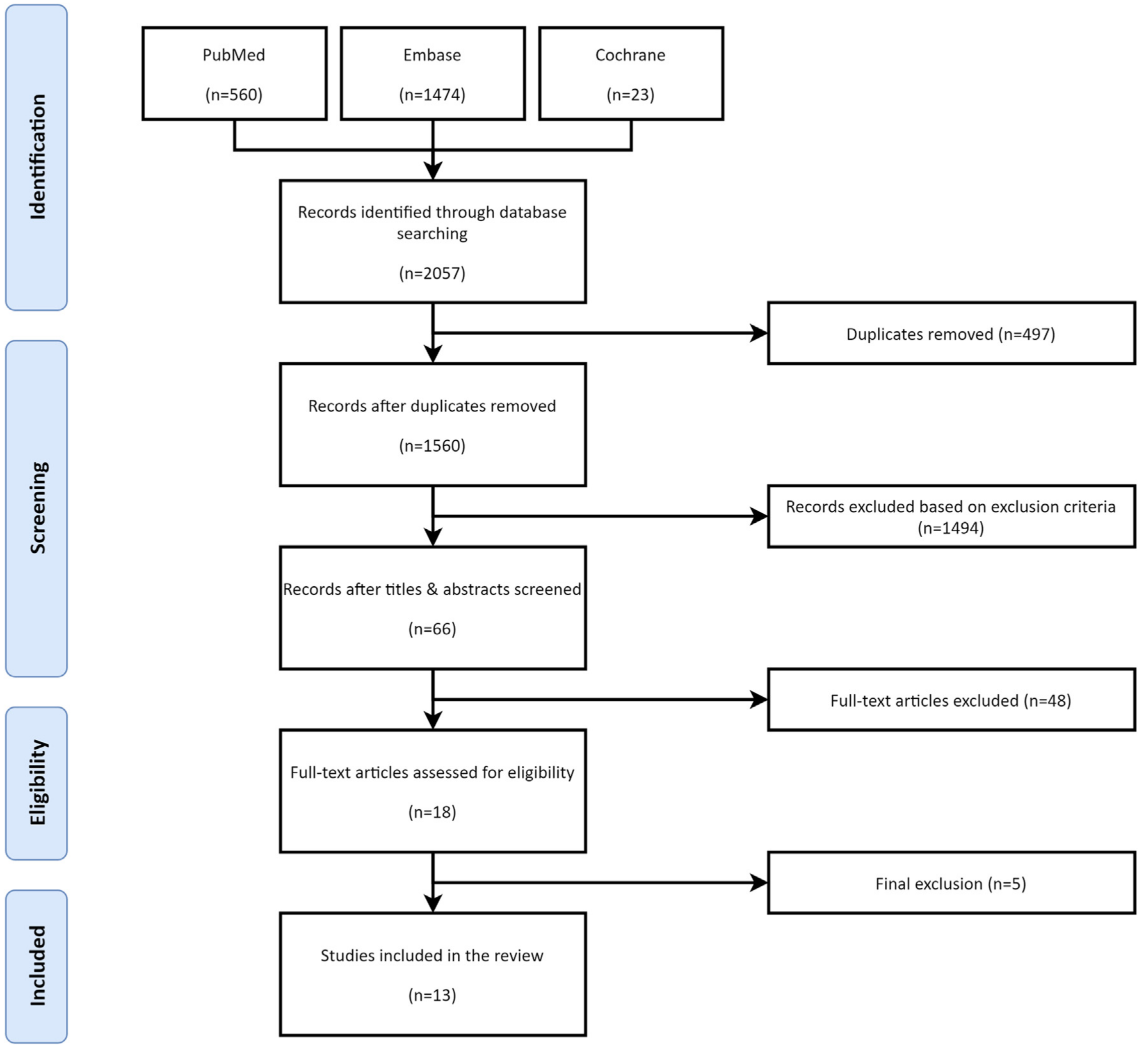

Fig. 1. PRISMA flow diagram showing selection of articles for review.

at more than one follow-up moment[15,16,18,19,21–23,25,26] and the other four studies only presented clinical cure rates at more than one follow-up moment.[14,17,20,24]

Of the nine studies reporting BP measurements at multiple follow-up moments, most showed little or no change in BP on group level at the second follow-up moment compared to the first follow-up moment, which was often at or within one month.[14,16,18–20,22–25] Overall, during the postoperative follow-up period most of the decrease of SBP occurred within the first months after adrenalectomy (Fig. 2). Thereafter, SBP often remained stable (8/9 studies).[16,18,19,21–23,25,26]

Clinical cure was defined as normotensive (SBP<140 mmHg/DBP<90 mmHg) without the aid of AHT in most of the studies.[16–18,20,21,23–26] Favia et al., Nakada et al. and Gockel et al. had no clear definition for clinical cure of HTN.[14,15,22] Lo et al. defined HTN as SBP>160 mmHg or DBP>95 mmHg or on AHT.[19] All but one study[15] reported the clinical cure rate at long-term follow-up, which varied from 13.6% to 77%. Fukudome et al. and Iacobone et al. showed a considerable decrease of the clinical cure rate on long-term compared to early follow-up at 23.8 days (74%–44%) and six months (66.7%–44.5%) postoperative, respectively.[20,26] Favia et al. and Citton et al. showed a lesser decrease of the clinical cure rate on long-term compared to earlier at eight days (78%–74%) and one month (38%–31%) postoperative, respectively.[14,18] Wachtel et al. and Wierdak et al. reported a slight increase of clinical cure rate on long-term compared to earlier follow-up (6.5%–13.6% and 11.3%–13.6%, respectively),[16,17] and Waldmann et al. reported a large increase in clinical cure rate on long-term compared to postoperative (37%–57%).[24]

Discussion

In this study, the course of postoperative BP-related outcomes after adrenalectomy in patients with PA have been systematically reviewed in currently available literature, and subsequent conclusions for outcome assessment and follow-up of BP were drawn based on best-available evidence. This systematic review shows that there is a large variety in studies reporting trends in BP-related outcomes with often insufficient methods of BP measurements and outcome data. This might reflect the lack of generally accepted guideline recommendations and variety in postoperative follow-up in daily practice. However, based on the available data at hand, one might argue that outcome assessment after adrenalectomy in patients with PA can be accurately performed within the first few weeks or months and it is expected that the effect of surgery on BP will remain stable over the long-term postoperative period.

Regarding BP measurements, most studies did not clarify their measurement methods (e.g. setting, protocol, frequency,

Table 1
Characteristics of the included studies.

Study, Year, Ref.	Country, City	Study type	Inclusion period	Included (n)	Diagnostics Used	Imaging Used (%)	Pathology results (%)*	Median Follow-up in Months [range]†
Favia 1992[14]	Italy, Padua	Retrospective cohort	1975–1989	52	PRA, PAC, PPC, ARR Saline-infusion test Captopril test Postural changes	CT (55.7) AVS/Venography (28.8) SNS (53.8)	APA (92.3) BAH (3.8) Other (3.8)	77 [13–189]
Nakada 1995[15]	Japan, Yamagata	Retrospective cohort	–	22	PRA, PAC, PPC, UAC	CT (100) SNS (100) AVS (-)	APA (100)	60 *mean*
Lo 1996[19]	China, Hong Kong	Retrospective cohort	1983–1994	46	PRA, PAC, PPC, UAC Postural changes	CT (100) AVS (24)	APA (100)	51 [1–132] *mean*
Fukudome 2002[20]	Japan, Fukuoka	Retrospective cohort	1976–1998	46	PRA, PAC, PPC, glucocorticoid levels	–	APA (100)	138 [14–277] mean
Sywak & Pasieka 2002[21]	Canada, Calgary	Retrospective cohort	1992–2001	24	ARR, UAC Postural changes	CT (91.6) AVS/SVS (70.8) NP-59 (4.2)	APA (54.2) PAH (33.3) IHA (12.5)	42 [13–97] *mean*
Gockel 2007[22]	Germany, Mainz	Prospective cohort	1994–2004	40	PAC, PPC, UAC	CT (85) MRI (40) US (100)	APA (87.5) NAH (12.5)	45 [7–114]
Pang 2007[23]	Australia, Sydney	Prospective cohort	1995–2005	62	PRA, PAC, PPC	CT (-)	APA (83.9) IHA (12.9) AC (1.6) Unknown (1.6)	59
Waldmann 2011[24]	Germany, Giessen and Marburg	Retrospective cohort	1993–2009	54	PRA, PAC, PPC, ARR, UAC	CT (-) MRI (-) US (29.6) AVS (50)	APA (98.1) NAH (1.9)	49 *mean*
Van der Linden 2012[25]	France, Paris	Retrospective cohort	2001–2009	156	PRA, PAC, ARR	CT (100) AVS (56)	APA (63) UAL (12) BAH (6) Unknown (19)	6 [IQR 3–8]
Iacobone 2012[26]	Italy, Padua	Retrospective cohort	1990–2010	9	PRA, PAC, PPC, ARR Saline infusion test Captopril test	CT (-) MRI (-) AVS (100)	APA (100)	36 [12–264]
Wachtel 2014[16]	USA, Philadelphia	Retrospective cohort	1997–2013	85	PRA, PAC	CT (-) AVS (87.1)	APA (-) UAH (-)	36 [IQR 15–80]
Wierdak 2018[17]	Poland, Krakow	Prospective cohort	2004–2015	44	PRA, PAC, PPC,	CT (-) MRI (-) US (-) AVS (-)	APA (-) NAH (-)	76 *mean*
Citton 2019[18]	Italy, Padua	Prospective cohort	2014–2017	26	PRA, PAC, ARR Saline infusion test Captopril test	CT (-) MRI (-) AVS (-)	APA (100)	8 [6–13]

Abbreviations: RR, blood pressure; PRA, plasma renin activity; PAC, plasma aldosterone concentration; PPC, plasma potassium concentration; ARR, aldosterone-renin-ratio; UAC, urinary aldosterone concentration; CT, computed tomography; AVS, adrenal venous sampling; SNS, 75-Se-norcholesterol scintigraphy after dexamethasone suppression; NP-59, 1311-6-β-iodomethyl-norcholesterol scintigraphy after dexamethasone suppression; MRI, magnetic resonance imaging; US, ultrasound; APA, aldosterone producing adenoma; PAH, primary adrenal hyperplasia; IHA, idiopathic hyperplasia of the adrenal gland; NAH, nodular adrenal hyperplasia; AC, adrenal carcinoma; UAL, unilateral atypical lesions; BAH, bilateral adrenal hyperplasia; UAH, unilateral adrenal hyperplasia; IQR, inter quartile range.
* Outcome of pathology examinations after unilateral adrenalectomy.
† Means or medians as reported by the included studies together with their range or inter quartile range.
'-' is unknown or not specifically/detailed reported data.

Table 2
Risk of Bias assessment for cohort studies using the Quality In Prognosis Studies (QUIPS) tool.

Domain → Study ↓	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	7. Overall risk of bias
Favia 1992[14]	High	Low	High	High	High	High	High
Nakada 1995[15]	High	Moderate	High	High	High	Moderate	High
Lo 1996[19]	Moderate	Moderate	High	High	Moderate	Low	Moderate
Fukudome 2002[20]	High	Low	Moderate	High	Moderate	Low	Moderate
Sywak & Pasieka 2002[21]	Low	Moderate	High	Moderate	Moderate	Moderate	Moderate
Gockel 2007[22]	Low	Moderate	High	Moderate	Moderate	Low	Moderate
Pang 2007[23]	Moderate	High	High	High	High	Moderate	High
Waldmann 2011[24]	Moderate	High	High	High	Moderate	Low	High
Van der Linden 2012[25]	Low	Low	Low	Low	Low	Low	Low
Iacobone 2012[26]	High	Low	High	Moderate	High	Moderate	High
Wachtel 2014[16]	High	Low	Moderate	Moderate	Low	Low	Moderate
Wierdak 2018[17]	Moderate	Low	High	Moderate	Moderate	Low	High
Citton 2019[18]	Low	Low	Moderate	Moderate	Low	Low	Low

Table 3
Baseline blood pressures and postoperative outcomes during follow-up.
At each follow-up moment the use of antihypertensives during the blood pressure measurements is reported below the blood pressure values.

Study, Year, Ref.	Preoperative SBP/DBP in mmHg	First Follow-up	Second Follow-up	Third Follow-up	Latest Follow-up	Antihypertensives use
Favia 1992[14]	193 ± 4/117 ± 1.7 AHT unknown	T = 8 days 154 ± 1.8/97 ± 1.8 AHT unknown Cure rate: 78%			T = 13–189 months (median 77) AHT unknown Cure rate: 74%†	–
Nakada 1995[15]	128 ± 9 MBP AHT unknown	T = 1 month ≈ 121 MBP AHT unknown	T = 3 months ≈ 113 MBP AHT unknown	T = 12 months 94 ± 6 MBP AHT unknown	T = 60 months 92 ± 8 MBP AHT unknown	–
Lo 1996[19]	180 ± 13 [140–240]/108 ± 13 [70– 140] On AHT	T = 2–17 days (mean 4) ≈ 130 On AHT Cure rate: 98%			T = 1–132 months (mean 51) ≈ 129 On AHT Cure rate: 77%††	Mean AHT per patient: 1.2 on long-term
Fukudome 2002[20]	178 ± 3/103 ± 2 Without AHT	T = 23.8 days 127 ± 2/82 ± 1 AHT unknown Cure rate: 74%			T = 14–277 months (mean 138) AHT unknown Cure rate: 44%	–
Sywak & Pasieka 2002[21]	164 (CI 153, 176)/98 (CI 90,106) On AHT	T = 6 months 134 (CI 129, 140)/85 (CI 81, 89) On AHT			T = 13–97 months (mean 42) 134/84 On AHT Cure rate: 35%	35% without AHT 52% reduction AHT 13% no change or increased AHT Long-term
Gockel 2007[22]	147 [110–210]/90 [60–120] On AHT	T = 5.5 days 140 [100–180]/80 [70–110] On AHT			T = 7–114 months (median 45) 140 [110–170]/90 [70–110] On AHT Cure rate: 36.8%†	36.8% without AHT 23.7% reduction AHT 26.3% no change or switch AHT 13.2% increased AHT Long-term
Pang 2007[23]	149 (CI 144, 154)/89 (CI 85, 92) On AHT	T = 1 month (median) 134 (CI 129, 138)/83 (CI 81, 85) AHT unknown			T = median 59 months 131 (CI 129, 134)/79 (CI 76, 82) On AHT Cure rate: 34%	Mean AHT per patient: preop 2.6 (CI 2.3, 2.9) vs postop 1.4 (CI 1.0, 1.7) 34% without AHT 57% improved control with AHT 9% no change or increased AHT Long-term
Waldmann 2011[24]	171 ± 32/99 ± 15 On AHT	T = post-op 134 ± 14/81 ± 7 On AHT Cure rate: 37%			T = mean 49 months On AHT Cure rate: 57%	Mean AHT per patient: preop 2.9 ± 1.5 vs postop 1.4 ± 1.5
Van der Linden 2012[25]	149 [IQR 135–160]/91 [IQR 83–97] On AHT	T = 15–90 days 130 On AHT	T = 3–6 months 125 On AHT	T = 7–12 months 132 On AHT	T = >12 months 127 On AHT Cure rate: 44% (median 6 [IQR 3–8] months)	Median AHT per patient: preop 2 [IQR 1–3] Adjusted RR medication*: 133 SBP
Iacobone 2012[26]	177 ± 26/94 ± 13 On AHT	T = 6 months 137 ± 11/83 ± 7 On AHT Cure rate: 66.7%			T = 12–264 months (median 36) 140 ± 14/84 ± 10 On AHT Cure rate: 44.5%	Mean AHT per patient: preop 2.6 ± 0.9
Wachtel 2014[16]	152.5 ± 21.1 On AHT	T = 2–3 weeks 136.2 ± 16.8 On AHT	T = 6–12 months 128.4 ± 11.2 On AHT Cure rate: 6.5%		T = IQR 15–80 months (median 36) 129.9 ± 14.9 On AHT Cure rate: 15.3%	Mean AHT per patient: preop 3.5 ± 1.5 vs 1.8 ± 1.5, 2.4 ± 1.4, 1.9 ± 1.5 postop respectively
Wierdak 2018[17]	–	T = 6 months On AHT Cure rate: 11.3%			T = 24 months On AHT Cure rate: 13.6%	Mean AHT per patient: preop 2.4
Citton 2019[18]	154 ± 19/91 ± 12 On AHT	T = 1 month 130 ± 15/78 ± 9 On AHT Cure rate: 38%			T = 6–13 months (median 8) 129 ± 13/79 ± 8 On AHT Cure rate 31%	Mean AHT per patient: 3.4 ± 1.5 preop to 1.2 ± 1.1, 1.3 ± 1.2 postop respectively

AbbreviationsSBP, systolic blood pressure; DBP, diastolic blood pressure; AHT, antihypertensives; T, timing of follow-up moment postoperatively; MBP, mean blood pressure; preop, preoperatively; postop, postoperatively; IQR, inter quartile range; CI, confidence internal.
* Authors adjusted the postoperative systolic blood pressure measurements using a formula including number of drug classes, systolic blood pressure preoperatively and serum sodium concentration preoperatively.
† No definition for cure; †† Hypertension was defined as SBP >160 mmHg or DBP >95 mmHg or on AHT.
Definitions.
- Long-term: latest follow-up. In all cases the mean or median follow-up reported in Table 1.
- Cure rate: complete clinical success rate – SBP below 140 mmHg and DBP below 90 mmHg without the use of antihypertensives.

- ± = standard deviation.
- [-] = range or inter quartile range.
- () = confidence interval.
- '-' is unknown or not specifically/detailed reported data.

repetition). Van der Linden et al. was the only study with clearly defined measurement methods.[25] Thirteen studies reported at least two postoperative BP measurements and/or clinical cure rates, of which three had data at more than two follow-up moments.[15,16,25] Nine studies showed significant decrease of SBP measured within the first months after surgery, of which most studies measured SBP at or within one month post-surgery.[14,16,18–20,22–25] These studies had their first postoperative follow-up moment starting from directly postoperatively to 15–90 days (range) after adrenalectomy. Two studies had their first measurement at six months postoperatively, also showing a major decrease in SBP and DBP.[21,26] One study showed the biggest decrease in BP after three months[15] and one study only reported clinical cure rates.[17] So, the biggest effect of adrenalectomy in patients with PA is seen within the first month postoperatively and presumably most of the effect occurs within the first few weeks after adrenalectomy. This reduction in BP confirms the widely known effect of adrenalectomy on BP.[3,27,28] However, the main objective of this review was to elucidate the postoperative trends of BP-related outcomes and, thereby, provide evidence for the necessary duration of follow-up to adequately perform outcome assessment. Eight studies showed that the BP after adrenalectomy remains stable over long-term postoperative period, which was often more than a year.[16,18,19,21–23,25,26] Of all the studies, Nakada et al., Van der Linden et al. and Wachtel et al. were the only studies with three or more postoperative follow-up moments, which should reflect a more accurate trend.[15,16,25] Van der Linden et al. showed that on group level SBP remained stable up to a year after their first follow-up moment, which was between 15 and 90 days. In addition, Wachtel et al. showed that the biggest decrease in SBP was seen at their first follow-up moment between 2 and 3 weeks. Thereafter, SBP only slightly decreased further between 6 and 12 months follow-up and remained stable at long-term (median 36 months). These results are emphasized by the low risk of bias and moderate risk of bias of Van der Linden et al. and Wachtel et al., respectively.[16,25] On the contrary, Nakada et al. showed a further decrease in MBP during follow-up up to one year, although the biggest decrease in MBP was shown within the first 3 months (13%), MBP additionally decreased between 3 and 6 months (8%) and 6–12 months (7%). However, these results must be interpreted carefully due to high risk of bias in this study. Moreover, Citton et al., another study with a low risk of bias, showed stable SBP and DBP after first follow-up at 1 month up to a median follow-up at 8 months.[18] Thus, based on these results one might argue that outcome assessment after adrenalectomy in patients with PA can be accurately performed within the first few weeks or months and it is expected that the effect of surgery will remain stable over the long-term postoperative period. Another study showed stable BP at 1 to 2, 3 to 4 and 5–6 years postoperatively.[29] In line, Nakada et al. showed stable MBP 1–5 years postoperatively.[15] Together, these studies with long-term follow-up underline our findings with stable BP.

We investigated the trends of clinical cure rates as well. Several studies did not define clinical cure[14,15,22] or wielded a deviating definition for clinical cure[19] compared to the PASO criteria of complete clinical success. Eight studies reported clinical cure rates at two different follow-up moments,[14,16–20,24,26] which was a short-term one and a long-term one in most of the studies. There was no clear trend in the course of the clinical cure rates in these studies: three studies showed clinical cure rates which remained almost stable over long-term period,[14,17,18] three studies had a clear

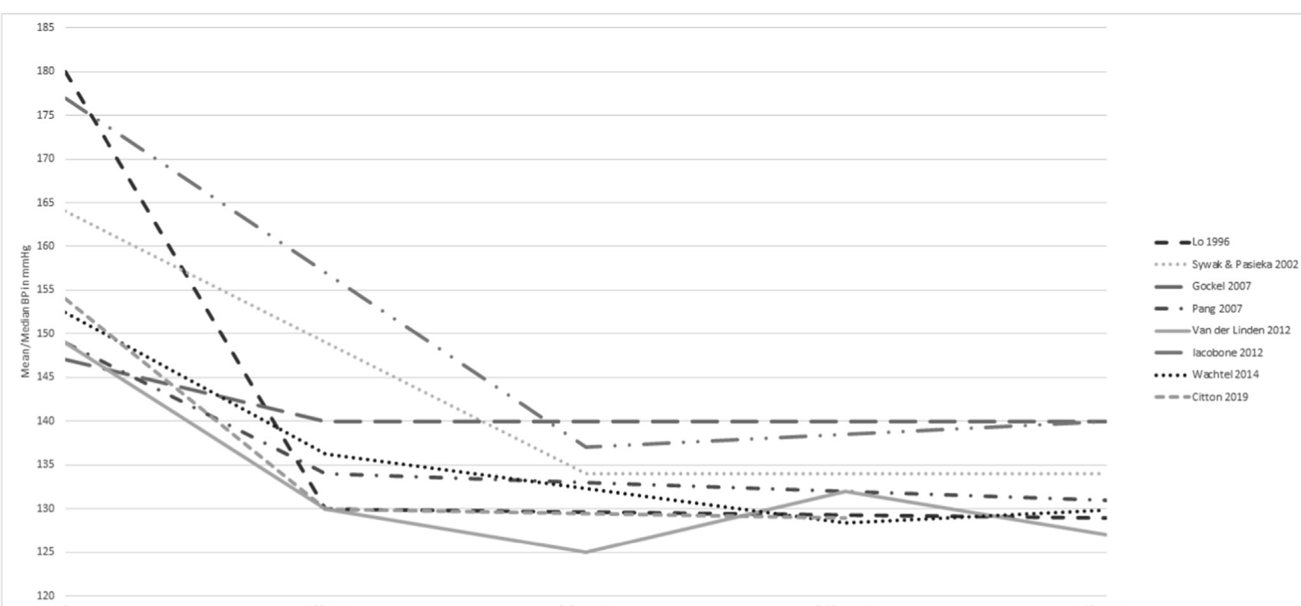

Fig. 2. The reported mean or median systolic blood pressure measurements of eight studies plotted in time. This line graph visualizes the trend of SBP decrease in the first few weeks to months after adrenalectomy. Eight of the thirteen studies are plotted, because these eight studies had mean or median SBP measurements at two or more follow-up moments. The x-axis is divided in four timeslots and for each study and each follow-up moment the data was added to their corresponding timeslot. Timeslot 'zero' is the preoperative SBP.Some remarks: Lo et al., Sywak & Pasieka, Pang et al., Iacobone et al., Wachtel et al. and Citton et al. reported their SBP in means.- Gockel et al. and Van der Linden et al. reported their SBP in medians.- It is assumed that all BP measurements were measured without discontinuing AHT.

decrease in clinical cure rates[19,20,26] and two studies showed an increase in clinical cure rates during the course of follow-up.[16,24] Moreover, 12 studies reported long-term clinical cure rates which were often lower than expected compared to their corresponding SBP and DBP reported at long-term.[14,16–26] This probably implies that a lot of patients were still in need for AHT to maintain well-regulated BP at long-term follow-up and did not fit the PASO criteria of complete clinical success. The goal of adrenalectomy is to correct aldosteronism and subsequently correct blood pressure. The former has biochemical success rates of approximately 90–100%, whereas the latter is often improved by surgery although cure of HTN is not always achieved. Two main reasons for failure of complete cure of HTN is underlying primary HTN and misdiagnosis. Especially in cohorts followed for multiple years – as is the case in these studies – primary HTN will have influence on the long-term clinical success rates.[30,31] Additionally, primary hypertension could also already be present at the time of diagnosis of PA, which will influence short-term outcomes. Furthermore, 0–10% of the patients has failure of biochemical cure and are probably misdiagnosed with PA. Consequently, a lower rate of complete clinical success is achieved as well.

AHT use is directly correlated to BP. Yet, the use of AHT (including mineral corticoid receptor antagonists) was in most studies often underreported. So, one may ask if BP really remains stable on long-term or that this is masked by raised or decreased AHT usage. Thereby, the increase of BP and the increased need for AHT is expected in a population which is sometimes followed for years, which probably shows the influence of primary HTN and/or end organ damage. We reviewed 13 studies of which only three studies reported the percentages of individual patients who had changes in their medication postoperatively, which were also reported differently.[21–23] Frequently nothing was stated about preoperative or postoperative AHT use during BP assessment. Presumably AHT were not discontinued if not clearly stated. This challenges the objective interpretation of BP decrease in these studies. Therefore, prospective studies are demanded to investigate the course of postoperative BP measurements, taking AHT usage into account. AHT usage should be reported in detail: e.g. what kind of AHT, the dose of AHT, changes in AHT compared to previous visits, on or off AHT during BP measurements, and the use of a wash-out period. Furthermore, this systematic review shows that the effect of adrenalectomy on BP can be determined shortly after with minimal changes in BP on long-term. Nevertheless, patients should be adequately treated with AHT when there is persistent HTN after adrenalectomy.

To our knowledge this is the first systematic review assessing the trends of BP-related outcomes after unilateral adrenalectomy for PA, including a comprehensive systematic literature search and quality assessment of the included studies according to a widely accepted tool. Nevertheless, the included studies had several limitations. A limitation of the thirteen included studies is that most of them are retrospective studies[14–16,19–21,24–26] which are subject to selection bias (e.g. lost to follow-up or selective exclusion due to missing data) or information bias (e.g. no standardized protocol or different measurement methods). Most studies were brief in the reporting of inclusion and exclusion criteria, consecutiveness of their cohort and adequate participation of eligible patients. Furthermore, several studies excluded patients based on missing data beforehand, which led to doubtful scores of low risk of bias in the domain 'study attrition'.[16,17,20,24–26] Thereby, definitions for BP-related outcomes, and standardized measurements of these outcomes were sometimes partially or not clearly reported. A recently published systematic review by Lenders et al. showed that this is a common problem in literature reporting BP after adrenalectomy for PA.[32] Furthermore, 8 out of 13 studies had less than 50 included patients with PA which limits the statistical power of these studies.[15,17–22,26] Another limitation may be the inclusion width of more than 40 years of the included studies, whereby diagnostics and imaging used during work-up vary among them. Especially the use of AVS might have influenced the results. AVS could be used to differentiate unilateral APA from bilateral hyperplasia or non-functioning adenoma. Within the included studies, AVS was used in 10 out of 13 studies and the percentage of patients with AVS ranged from 24 to 100 (Table 1). This might have led to differences in clinical cure rates. However, internationally controversy remains regarding the added value of routine use of AVS in all patients.[33,34] Furthermore, the use of AVS in daily clinical practice shows significant variability in expert centers.[35] Moreover, all studies primarily reported data on group level and we did not actively contact authors for individual patient data, which is expected to be favorable with considerable advantages (e.g. subgroup analysis or adjustment for confounding factors), over group level data.[36] On the other hand, the studies of Van der Linden et al. and Citton et al. were properly performed and had overall low risk of bias which emphasize their outcomes and, thereby, these studies may invigorate our conclusions.[18,25] Another limitation of our study may be that we did not focus on biochemical outcome data (e.g. plasma aldosterone, plasma renin, plasma potassium, and aldosterone-renin-ratio). Beforehand, we chose to examine the clinical outcome parameters used for the complete clinical success rate as stated by the PASO study. Nevertheless, biochemical outcomes are closely linked to improvement of blood pressure control, since complete biochemical success rates after adrenalectomy have been reported at approximately 90–100%.[3–5] Of the 13 studies included in this review, three studies[17,18,26] reported complete biochemical success in all operated patients and one study[24] in all patients in which postoperative biochemical measurements were performed (Supplementary Table 2). Furthermore, seven studies reported postoperative potassium outcomes and reported normalization in 98–100% of patients (Supplementary Table 2).[14,17–19,22,24,26]

Based on our results we would like to present several recommendations regarding outcomes and follow-up after surgery for PA. Preoperative counseling is important to manage expectations of the patients, because complete cure of HTN is no certainty. In this systematic review, we have seen that the biggest effect of adrenalectomy on blood pressure is reported within in the first month after surgery and often remains stable during long-term (median 6–59 months) follow-up. Therefore, we propose to perform initial clinical outcome assessment at or within one month postoperatively. Further visits during follow-up should be tailored according to the initial assessment. Complete biochemical success is expected to be accurately assessed a few days to a week after surgery. So, biochemical outcome assessment may be performed during initial admission or at the one-month clinical outcome assessment. The following follow-up algorithms may be of added value, although it should be noted that the included studies show no direct evidence for these suggestions, in addition to the already mentioned varying methodological quality of these studies. Patients with complete clinical success may not need intensive follow-up and could be followed-up with longer intervals or maybe discharged from follow-up (e.g. 1 month–6 months – 12 months – annually). In the case of partial clinical success – decreased BP or normalized BP with the need for AHT – one might apply a tighter follow-up regime with shorter intervals during the first year to adjust and tailor AHT medication (e.g. 1 month–3 months – 6 months–9 months–12 months). Patients with absent clinical success should be followed at short intervals, for example monthly for the first half year. These patients may be subjected to further diagnostics to determine the underlying cause of persisting HTN.

Conclusions

There is a significant decrease of BP within the first weeks or months after adrenalectomy and multiple studies suggest that after this decrease, the BP remains stable during long-term follow-up. Therefore, based on current literature, one could argue that clinical outcome assessment after adrenalectomy in patients with PA can be accurately performed within the first month(s) postoperatively. Nevertheless, it must be taken into account that follow-up practices and methodological quality varies widely between currently available literature. Particularly AHT usage was poorly reported and not standardized, thereby hampering the interpretation of blood pressure stability during follow-up.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2020.12.003.

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