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Outcome of adrenalectomy for unilateral primary aldosteronism: International consensus and remission rates

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Contributors

TAW, JWML, PM, CEG-S, JF and M. Reincke designed the study; TAW, CEG-S, JF and M. Reincke interpreted the responses from the questionnaires; JWML, PM, JB, CA, FS, LA, MQ, JD, FB, KKK, UP, RM, HU, AP, TK, MN, MS, TN and WFY Jr collected data; TAW, JWML, PM, JB, CA, FS, LA, MQ, JD, FB, KKK, UP, RM, HU, AP, TK, MN, MS, TN, WFY Jr and M. Reincke assessed outcome rates; JB and M. Rottenkolber performed statistical analyses; TAW, JWML, JF, CEG-S and M. Reincke wrote the first draft of the manuscript. All authors made critical revisions of the manuscript. A complete list of contributors is provided in the appendix.

Declaration of Interests

WYF declares a consulting agreement with Nihon Medi-Physics

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Abstract

Background—Although unilateral primary aldosteronism is the most common surgically correctable cause of hypertension there are no standard criteria to classify surgical outcomes.

Methods—The Primary Aldosteronism Surgical Outcome study reached consensus by an international panel of 31 experts, including 6 endocrine surgeons, using the Delphi method. On the basis of standardised criteria, remission (complete, partial, absent) rates for clinical and biochemical outcomes were determined in retrospective cohorts (n=30-99) of consecutive patients unilaterally adrenalectomized based on adrenal venous sampling from 12 tertiary centres in 9 countries over 4 continents.

Findings—Consensus was reached for 6 criteria of clinical and biochemical outcome and 2 recommendations for follow-up. Complete clinical success was achieved in 37% of patients, with a wide variance (17-62%), and partial clinical success in an additional 47% (35-66%); complete biochemical success was seen in 94% (83-100%). Female patients had a higher likelihood of complete clinical success (OR=2.25; 95% CI, 1.40-3.62) and clinical benefit (complete + partial clinical success) (OR=2.89; 95% CI, 1.49-5.59). Younger patients had a higher likelihood of complete clinical success (OR=0.95 per extra year; 95% CI, 0.93-0.98) and clinical benefit (OR=0.95 per extra year; 95% CI, 0.92-0.98). Higher levels of pre-operative medication were associated with lower levels of complete clinical success.

Interpretation—Standardised outcome criteria are relevant for evaluating the quality of surgical treatment in individual patients and will allow the comparison of outcome data in clinical and scientific studies. The baseline clinical characteristics of a cohort contribute to the wide variation in clinical outcome rates. A majority of patients derive clinical benefit from adrenalectomy with younger patients and female patients likely to particularly benefit from a favourable surgical outcome. Screening for primary aldosteronism should nonetheless be performed in every individual fulfilling the Guideline criteria, since biochemical cure is by itself clinically important and older women and men may also derive post-operative clinical benefit.

Introduction

Primary aldosteronism (PA) is a form of endocrine hypertension characterized by inappropriately high plasma aldosterone concentrations relative to suppressed plasma renin (1). The prevalence of PA is reported as 5% in the general hypertensive population (2) increasing to 10% in referred populations and to 15-20% in patients with treatment-resistant hypertension (3), although estimates vary widely (4). Several studies have demonstrated higher cardiovascular and cerebrovascular morbidity and mortality rates in patients with PA compared with age-, sex- and blood pressure matched patients with essential hypertension (5–8) with resolution of excess risk following surgical or specific medical treatment (9–10). Thus early diagnosis and appropriate treatment of PA is essential to minimize the increased risk associated with this condition.

PA is classified into unilateral and bilateral forms of the disease which must be distinguished because though the former may respond well to adrenalectomy the latter is treated with mineralocorticoid receptor antagonists (11). Although adrenal venous sampling is the recommended procedure to distinguish PA subtypes (11), it is not widely available, so that for lateralisation some centres rely on computed tomography or magnetic resonance imaging.

Surgical treatment of unilateral PA should resolve the excessive aldosterone secretion in all patients. Consequently, persisting primary aldosteronism following adrenalectomy suggests that the initial diagnosis was incorrect with the patient having bilateral rather than unilateral PA. To define post-surgical outcomes, specific clinical and biochemical criteria are required for persistent or recurrent disease. There is wide variation in reported clinical remission rates between centres (16-72%) that are attributed to several underlying factors such as background primary hypertension, age, long-standing PA, advanced renal failure or other co-morbidities (12–15). Heterogeneity, however, may also reflect the absence of standardised criteria to classify outcomes of adrenalectomy for unilateral PA. We thus hypothesised that standardised uniform outcome criteria applied across a large multi-centre patient cohort might minimize the previously reported variation in outcome results. Such uniform criteria might not only improve clinical care of PA patients but also serve as the basis of comparing outcome data from different clinical centres.

The objectives of our Primary Aldosteronism Surgical Outcome Study (PASO) study were: 1) to establish international consensus for a set of standardised criteria on clinical and biochemical outcome of adrenalectomy for unilateral PA; 2) to apply these criteria to follow-up data in a large multicentre cohort of PA patients from different clinical expert centres to calculate international remission rates; 3) to identify the preoperative determinants of successful outcome and 4) to determine the extent to which these may explain differing complete success rates across centres.

Methods

Consensus building by the Delphi technique

The Delphi technique (16) was used to reach a consensus for six outcome criteria of adrenalectomy for unilateral PA: complete success (remission), partial success (improvement) and absent success (persistence) for both clinical and biochemical outcome and recommendations for the time and interval of follow-up. Because clinical and biochemical outcome results in PA are not *a priori* linked and could depend on different pre-operative factors, these outcome parameters were assessed and analysed separately.

The Delphi method employs a series of questionnaires sent to participants selected for their expertise, wide geographical representation and for this study, surgical representation. All communication was by email and replies monitored by two core group members who did not respond to the questionnaires. The Delphi process required 4 rounds of questionnaires with strict criteria to pass consensus at each round (figure S1) (16). Participating centres are shown in table S1, with 31 respondents (including 6 endocrine surgeons) from 28 centres,

with 3 centres providing individual responses from 2 participants each (Torino, Paris and Nijmegen).

Application of the consensus criteria to assess outcome

We approached 15 centres of expertise to contribute patient data, an invitation that 12 of them were able to accept. Clinical and biochemical outcome rates, defined as complete, partial or absent success, were assessed in the 12 referral centres over 4 continents. The data were collected within the prospective registries and all patients gave written informed consent for the use of data. For this, consecutively adrenalectomized patients were included from each centre with follow-up data for outcome assessment (table 1). Only patients diagnosed with unilateral PA by adrenal venous sampling were included in the study and all centres used total adrenalectomy as the surgical procedure for the treatment of unilateral PA.

PA was diagnosed according to the Endocrine Society Guideline (11) or the Japan Endocrine Society Guideline (17). Measurement of biochemical and clinical parameters and adverse events following surgery are shown in the supplemental appendix. Each centre applied the clinical and biochemical outcome criteria to their patients and all outcome rates were calculated at 6-12 months according to the criteria for the assessment of final outcome established by the PASO consensus (table 1). Outcome rates were assessed by each centre and cross-checked by members of the core group. Amendments were returned to participating centres for double-checking. In addition to the outcome categories as defined in Table 1 (complete, partial and absent success), we assessed clinical and biochemical benefit which we defined as the complete and partial success categories combined.

Statistical analyses

IBM SPSS software version 22 was used for all statistical analyses unless otherwise stated. The overall outcome rates were calculated considering the number of patients per centre and are shown as proportions. All quantitative normally distributed variables are reported as mean $\pm$ standard deviation; quantitative non-normally distributed variables are presented as median with lower and upper quartiles. Categorical variables are presented as absolute numbers and percentages. One-way ANOVA with *post hoc* Bonferroni analysis was used for quantitative normally distributed variables. Analysis of group differences used Kruskal-Wallis or Mann-Whitney-U tests for quantitative non-normally distributed variables and the chi-square or Fisher's exact tests for categorical variables. Logistic regression analysis was performed at the patient level to identify determinants of clinical and biochemical outcome. Centre-effects were accounted for with a fixed-effect model using logistic Regression Program R and multilevel modelling was performed by fitting logistic regression models with centre as random effects using IBM SPSS statistics software version 22.

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The funding source had no role in study design, data collection, data analysis or interpretation or manuscript writing. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Consensus for outcome of adrenalectomy for unilateral PA

Consensus was reached for a set of standardised criteria for complete, partial and absent clinical and biochemical success based on blood pressure, use of antihypertensive drugs, and plasma potassium, aldosterone and renin (table 1). In terms of follow-up interval, the consensus view was that the first post-surgical outcome assessment of at least blood pressure and plasma potassium should be carried out within the first 3 months to adjust antihypertensive medication and correct hypo- or hyperkalemia if required. Final outcome (blood pressure, plasma potassium, plasma aldosterone and plasma renin) should be assessed at 6-12 months after adrenalectomy and reassessed at yearly intervals to exclude persistence or reoccurrence of the disease.

International remission rates for unilateral PA

The consensus criteria were used to assess remission rates in 12 international expert clinical centres (table S1) each contributing 30-99 consecutively operated (unilateral laparoscopic adrenalectomy) patients with adequate follow-up data to assess outcome (total number of patients=705). The period of patient inclusion and the numbers of patients diagnosed with unilateral PA during the same period are shown in table S2.

Across the 12 centres complete clinical success rates varied widely in contrast with consistently high biochemical success rates (figure 1A, 1B); clinical and biochemical data were available for 699 of 705 patients (6 patients lacked adequate biochemical follow-up). Complete biochemical success was seen in 94% of patients (656/699; range 83-100%) whereas the complete clinical success rate was only 37% (259 of 705 patients; range 17-62%) (figure 1C). Improvement in blood pressure control (partial clinical success) was attained in a further 47% of patients, resulting in normalisation or improvement in blood pressure in over 4 of every 5 patients.

Different protocols of AVS were used between centres (table S3). We therefore compared outcome rates and baseline characteristics of patients after subdivision according to AVS procedure (unstimulated compared with adrenocorticotrophic hormone-ACTH 1-24-stimulation) or interpretation (lateralisation index <4 or ≥ 4). Clinical outcome was not significantly affected by the use of an unstimulated or stimulated AVS protocol (table S4) or by a lateralization index <4 or ≥ 4 (table S5).

Tables 2 and 3 and table S6 show unadjusted baseline data of the combined centres for clinical and biochemical outcomes; table S3 shows equivalent data for each referral centre. For the pooled data, we show significant differences between unadjusted clinical outcomes for 19/25 measurements (table 2). For biochemical outcomes, there were fewer differences: plasma aldosterone, creatinine, lateralisation index, contralateral suppression, contralateral ratio <1 and adrenal nodule size (table 3). Unadjusted analyses of complete success compared to partial and absent clinical success rates combined, and complete and partial rates combined (clinical benefit) compared with absent clinical success rates are shown in tables S7 and S8, respectively.

Correlates of clinical and biochemical outcome were analysed by assessing odds ratios in unadjusted and adjusted analyses (table 4). Independent correlates of complete success were identified in an adjusted analysis by comparing complete success rates with partial and absent success rates combined (table 4). Baseline systolic blood pressure was the only independent correlate of complete biochemical success: patients with higher blood pressure had an increased likelihood of complete success (OR=1.03; 95% CI, 1.01-1.05) (table 4A). Complete clinical success correlated with four variables: female sex (OR=2.25; 95% CI, 1.40-3.62), lower age (OR=0.95 per extra year; 95% CI, 0.93-0.98), fewer antihypertensive medications as measured by defined daily dose (OR=0.80 per unit increase; 95% CI, 0.70-0.90) and absence of left ventricular hypertrophy (OR=1.61; 95% CI, 1.01-2.59) (table 4A).

Five independent correlates of clinical benefit were identified by comparing complete and partial success rates combined with absent success rates (table 4B). Female sex (OR=2.89; 95% CI, 1.49-5.59), younger age (OR=0.95 per extra year; 95% CI, 0.92-0.98) and lower BMI (OR=0.90 per unit increase; 95% CI, 0.85-0.96) were independent determinants of clinical benefit. Patients with higher SBP levels (OR=1.03 per mmHg; 95% CI, 1.01-1.04) and higher antihypertensive medication at baseline (OR=1.27 per unit increase; 95% CI, 1.08-1.50) were also more likely to obtain clinical benefit from adrenalectomy (table 4B).

In a comparison of complete with absent success, lower age (OR=0.92 per extra year; 95% CI, 0.88-0.96) and female sex (OR=4.48; 95% CI, 2.10-9.60) correlated with clinical success and BMI was inversely correlated with clinical (OR=0.91 per unit increase; 95% CI, 0.85-0.97) and biochemical success (OR=0.88 per unit increase; 95% CI, 0.79-0.99) (table 4C).

Gender distribution varied widely from 24 to 60% female, with 9 centres enrolling more men than women. Notwithstanding this bias, 11 of the 12 reported more women than men showing complete clinical remission with 55% of women *versus* 22% of men achieving complete clinical success whereas a greater proportion of men had partial or absent clinical success (partial success: 36% of women *versus* 56% of men; absent success: 9% of women *versus* 22% of men).

The average age at presentation ranged from 47.7±10.3 in Paris to 54.4±11.1 years in Sendai, a difference of almost seven years which may reflect differences in referral patterns. The average age of patients achieving complete clinical success was 46.4±10.5 years which was significantly lower compared with those patients achieving partial success (53.0±10.3 years, P<0.001) or with those patients who had an absent clinical outcome (54.5±10.0 years, P<0.001).

Adjustment for the confounding effect of centres demonstrated a marginal effect on female sex (OR=2.26; 95% CI, 1.36-3.77), younger age (OR=0.95 per extra year; 95% CI, 0.93-0.98) and lower antihypertensive medication (OR=0.72 per unit increase; 95% CI, 0.62-0.83) as correlates of clinical remission (table S9). Lower age remained a determinant of complete clinical success (OR=0.94 per extra year; 95% CI, 0.90-0.98) when the adjusted analysis was restricted to men (table S10).

We used multilevel modeling to analyse between-centre heterogeneity, when we built the model from centre up, it appeared that age and sex accounted for much of the heterogeneity across centres.

Discussion

We provide a consensus on criteria to define the outcome of adrenalectomy for unilateral primary aldosteronism, a consensus built using the Delphi method of iterative questionnaires to a panel of expert participants (16). This method is particularly appropriate to reach consensus on controversial themes with divergent published evidence. Central to this method is participant anonymity within the expert panel with communication via email to a monitoring group. This evades the emotionally charged atmosphere associated with renowned experts discussing complex issues, the effect of dominant individuals or of self-censorship. Further, because communication is by email, there are no restrictions on participant selection, theoretically allowing the inclusion of unlimited numbers of experts without geographical constraints.

Previous studies have reported the outcome of unilateral adrenalectomy for PA but divergent and ill-defined criteria with variable follow-up intervals have been employed to assess outcome (12, 18–23). Outcome results vary widely across studies and may under- or overestimate the real outcome effects. Remission of blood pressure has been reported in 20–72% of patients (12, 18) which is close to the results of our study (17–62%) that applied uniform criteria. Therefore this latter variability cannot be accounted for by lack of standardised criteria or differences in post-surgical follow-up protocols. However, using standardised criteria, we report more variation of biochemical outcome (83–100%) as compared to previously reported rates (96–100%) (12, 18), suggesting an overestimation of the real effects of adrenalectomy.

The utility of the consensus not only lies in the comparison of outcome data for clinical and scientific studies but also as a quality measure of patient diagnoses. Hence, complete biochemical success reflects the correct diagnosis and treatment of unilateral PA; the partial and absent biochemical success categories identify those patients with bilateral PA with asymmetrical bilateral aldosterone production rather than unilateral PA. Clinical outcome is not only dependent on biochemical outcome but also on other factors such as pre-existing primary hypertension, age, duration of hypertension and renal function.

Of the twelve centres submitting sequential complying studies in which the complete/partial/absent criteria were strictly observed: nine followed the Endocrine Society Guideline (11), and the other three that of the Japan Endocrine Society (17), in terms of pathways and procedures. No discernible differences were seen in following one guideline rather than the other. Analysis of individual and group data pinpointed three correlates of clinical success: age, sex and defined daily dose of anti-hypertensive medication. We show that younger patients have higher clinical remission rates and that women on average a better chance post-surgery of clinical remission than men. Young and female patients also displayed a higher likelihood of clinical benefit from surgery. Higher BMI was associated with an increased likelihood of absent clinical and biochemical success. The reason for this is unclear at

present but may be related to the higher aldosterone levels observed in patients with obesity (25).

Partial clinical success occurred in almost half of patients with an average decline in blood pressure of 24/11 mmHg. Such an effect also confers clinical benefit for the patient because a decrease in blood pressure, with or without a decrease in drug use, translates to improved long-term cardiovascular outcomes (26).

The finding of a marked gender difference presumably reflects the vasoprotective role of estrogens before menopause, lessening the likelihood of irreversible vascular damage. Similarly, the older the patient - male or female - the higher the likelihood of such damage and the higher the probability of associated primary hypertension. The results of biochemical outcome of adrenalectomy are principally determined by the correct diagnosis of unilateral aldosterone excess and a completely performed adrenalectomy. Removal of the source of aldosterone excess should thus normalise the biochemical abnormalities. In contrast, clinical outcome is not only dependent on normalisation of aldosterone secretion but also on the existing deleterious vascular and renal changes determined by the duration of the preceding aldosterone-induced hypertension.

Some strong features of our outcome study should be emphasised: clinical and biochemical outcome have been addressed separately; the criteria were stringently applied to a large international cohort of patients and every patient with the required outcome data could be systematically classified according to the Delphi-defined criteria; all patients were diagnosed for surgically amenable treatment by adrenal venous sampling. The main limitation of our study is that our database lacked hard endpoint outcomes and therefore we were unable to validate our surgical outcome criteria. This will be addressed in a prospective multi-centre validation study that is currently being planned which will include measures of cardiovascular morbidity and mortality. Additional limitations are the lack of ambulatory blood pressure monitoring at baseline and post-surgery to provide a more standardised assessment of BP response to adrenalectomy and the unavoidable use of arbitrary criteria to define improvement of blood pressure control in terms of reductions in antihypertensive medication.

In conclusion, the PASO (Primary Aldosteronism Surgical Outcome) consensus offers feasible criteria for classification of outcome of adrenalectomy for unilateral primary aldosteronism. The baseline characteristics of the cohort contribute to the wide variation in clinical outcome rates. Younger patients and female patients have a higher chance of complete clinical success and clinical benefit. However, screening should be performed in every individual fulfilling the Guideline criteria (11), since biochemical cure is by itself clinically important and also older women and men may derive post-operative clinical benefit; the data, however, help us to inform and counsel patients about the expectations following surgery based on age and sex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in tables

Abbreviation	Definition
N	Number of patients with outcome data
n	Number of patients with data for baseline characteristic (only cited when <N)
N.A.	Not applicable
n.d.	Not determined
HT	Hypertension
BMI	Body mass index
DRC	Direct renin concentration
ARR	Aldosterone to renin ratio
PRA	Plasma renin activity
ARR_DRC	ARR calculated using the DRC
ARR_PRA	ARR calculated using the PRA
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
DDD	Defined daily dose calculated according to ATC/DDD Index 2010: http://www.whocc.no/atc_ddd_index/ 2010
eGFR	Estimated glomerular filtration rate
LVH	Left ventricular hypertrophy, evaluated by echocardiography
LI	Lateralisation index, $([\text{aldosterone}]/[\text{cortisol}]_{\text{dominant adrenal vein}})/([\text{aldosterone}]/[\text{cortisol}]_{\text{non-dominant adrenal vein}})$

SI_RAV	Selectivity index_right adrenal vein, [cortisol] _{right adrenal vein} /[cortisol] _{peripheral vein}
SI_LAV	Selectivity index_left adrenal vein, [cortisol] _{left adrenal vein} / [cortisol] _{peripheral vein}
CLR	Contralateral ratio,([aldosterone]/ [cortisol] _{non-dominant adrenal vein})/([aldosterone]/ [cortisol] _{peripheral vein})
CL supp	Presence of contralateral suppression defined as contralateral ratio (CLR) <1
ILR	Ipsilateral ratio,([aldosterone]/[cortisol] _{dominant adrenal vein})/ ([aldosterone]/[cortisol] _{peripheral vein})

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Research in Context

Evidence before this study

Adrenalectomy is the recommended treatment for unilateral primary aldosteronism in patients willing and able to undergo surgery. Success rates in terms of biochemical remission are high across various reports (96-100%); in contrast, clinical remission has been reported for a much wider range (20-72%) of patients. This variability may be real, across centres, or may reflect lack of standardised criteria and/or differences in post-surgical follow-up.

Added value of this study

Our study is in two parts. First, using the Delphi method we were able to reach consensus, for six outcome criteria (complete, partial and absent success, clinical and biochemical) for unilateral adrenalectomy and two recommendations for the time and interval of follow-up. In an international multicenter study we applied these criteria to a large cohort of patients who underwent adrenalectomy. Complete clinical success rates ranged from 17-62%; complete biochemical success averaged 94%. Female sex and younger age were independent correlates of clinical success.

Implications of all the available evidence

This study sets a standard set of outcome criteria for unilateral primary aldosteronism. The criteria are relevant for evaluating the quality of surgical treatment in individual patients and for the comparison of outcome data in clinical and scientific studies. We identify younger patients and female patients with unilateral primary aldosteronism who are likely to have a favourable surgical outcome. These data will be useful for health care professionals to counsel patients with unilateral primary aldosteronism prior to adrenalectomy concerning the expected post-operative clinical benefit.

Figure 1.

Clinical (Panel A) and biochemical (Panel B) outcome rates, defined as complete (shaded columns), partial (white columns) and absent (black columns) success, were assessed according to the consensus (table 1) and are shown with patient numbers (n) indicated in parenthesis. The overall outcome rates of the combined cohort are shown as proportions with the ranges for each outcome group indicated in parenthesis (Panel C).

Table 1
Primary Aldosteronism Surgery Outcome international consensus

Outcome measure	Definition/recommendation
Complete clinical success	Normal blood pressure ¹ without the aid of antihypertensive medication
Partial clinical success	The same blood pressure ² with less antihypertensive medication ^{3,4} or a reduction in blood pressure with either the same amount or less antihypertensive medication
Absent clinical success	Unchanged or increased blood pressure levels ² with either the same amount or an increase in antihypertensive medication ^{3,5}
Complete biochemical success	Correction of hypokalemia ⁶ (if present pre-surgery) and normalisation of the ARR ⁷ . In patients with an elevated ARR, aldosterone secretion should be suppressed in a post-surgery confirmatory test ^{8,9}
Partial biochemical success	Correction of hypokalemia ⁶ (if present pre-surgery) and an elevated ARR ⁷ with one or both of the following (compared to pre-surgery): 1) 50% decrease in baseline plasma aldosterone level 2) abnormal but improved post-surgery confirmatory test result ⁹
Absent biochemical success	Persistent hypokalemia ⁶ (if present pre-surgery) and/or persistent elevated ARR ⁷ with failure to suppress aldosterone secretion with a post-surgery confirmatory test ⁹
Outcome assessment	Outcome assessment should first be performed in the 3 months post-surgery but final outcome should be assessed at 6-12 months
Annual re-assessment	Outcome should be reassessed annually ¹⁰

ARR, aldosterone-to-renin ratio; complete success, remission; partial success, improvement; absent success, persistence

¹Normal blood pressure as defined by the European Society of Hypertension Guidelines (24):

- a. Office or outpatient setting: systolic BP < 140 mmHg and diastolic BP < 90 mmHg
- b. Home BP: systolic BP < 135 mmHg and diastolic BP < 85 mmHg
- c. Daytime ABPM: systolic BP < 135 mmHg and diastolic BP < 85 mmHg
- d. 24 h ABPM: systolic BP < 130 mmHg and diastolic BP < 80 mmHg

²Blood pressure responses based on the differences between blood pressure levels that define the blood pressure categories of hypertension (24)

- a. Unchanged blood pressure levels defined as: a difference (pre- versus post-operatively) of systolic BP < 20 mmHg and diastolic BP < 10 mmHg
- b. Reduction or increase in blood pressure defined as: difference in systolic BP 20 mmHg and/or diastolic BP 10 mmHg.

NB If a change in systolic BP and an opposing change in diastolic BP is observed, the BP response is defined by the change in systolic BP.

³Antihypertensive medication is expressed as Defined Daily Dose which is the assumed average maintenance dose per day for a drug used for its main indication in adults (DDD; ATC/DDD Index 2010; http://www.whooc.no/atc_ddd_index/ 2010);

- a. Unchanged antihypertensive medication defined as: a change of ± 0.5 DDD compared to pre-surgery
- b. Less antihypertensive medication is defined as: a decrease of 0.5 DDD compared to pre-surgery
- c. Increased antihypertensive medication is defined as: an increase of 0.5 DDD compared to pre-surgery

- ⁴ Changes in antihypertensive medication should be measured when final outcome is assessed at 6-12 months according to the outcome assessment recommendation.
- ⁵ Reduction in blood pressure on increased antihypertensive medication is classed under the category of absent clinical success. The same applies to an increase in blood pressure on less antihypertensive medication
- ⁶ Hypokalemia is defined as serum potassium < 3.6 mEq/L
- ⁷ Normalisation of the ARR defined according to local laboratory reference intervals
- ⁸ If baseline plasma aldosterone is below the locally defined upper reference limit (URL) for a saline infusion or a fludrocortisone suppression confirmatory test then these tests (the saline infusion and the fludrocortisone suppression confirmatory test) are unnecessary even if the ARR is elevated (this corresponds to “hyporeninemic hypoadosteronism”)
- ⁹ Post-surgery confirmatory test results:
Complete biochemical success: normal suppression is defined as follows:
 - a. saline infusion test: plasma aldosterone <5 ng/dL (0.14 nmol/L)
 - b. oral sodium loading test: urinary aldosterone < 10 µg/24h at the Mayo Clinic (or defined according to local reference values)
 - c. captopril challenge test: a decrease in plasma aldosterone after captopril > 30%
 - d. fludrocortisone suppression test: day 4 upright 10 am plasma aldosterone level < 6 ng/dLPartial biochemical success: an abnormal but improved post-confirmatory test result is defined as follows:
 - a. saline infusion test: plasma aldosterone, 5-10 ng/dL (0.14-0.28 nmol/L)
 - b. oral sodium loading test: urinary aldosterone, 10-12 µg/24h at the Mayo Clinic (or defined according to local reference values)
 - c. fludrocortisone suppression test: positive but day 4 upright 10 am plasma aldosterone level at least 20% lower than pre-adrenalectomy.Absent biochemical success: failure to suppress aldosterone secretion is defined as:
 - a. saline infusion test: plasma aldosterone > 10 ng/dL (> 0.28 nmol/L)
 - b. oral sodium loading test: urinary aldosterone > 12 µg/24h at the Mayo Clinic (or defined according to local reference values)
 - c. captopril challenge test: a decrease in plasma aldosterone after captopril by 30%
 - d. fludrocortisone suppression test: day 4 upright 10 am plasma aldosterone level > 6 ng/dL
- ¹⁰ Annual re-assessment includes a minimum assessment of blood pressure and potassium levels

Table 2
Characteristics of patients with unilateral PA stratified for clinical outcome.

VARIABLE	Total cohort	CLINICAL SUCCESS			Overall P-value	Pairwise Comparison – P values		
		Complete	Partial	Absent		C vs P	C vs M	P vs M
Clinical Outcome	705	259 (36.8%)	334 (47.4%)	112 (15.9%)	N.A.	N.A.	N.A.	N.A.
Age (years)	50.8±10.9	46.4±10.5	53.0±10.3	54.5±10.0	<0.01	<0.01	<0.01	0.59
Female	311 (44.1%)	172 (66.4%)	113 (33.8%)	26 (23.2%)	<0.01	0.035	<0.01	<0.01
BMI (kg/m ²) (n=703)	27.6±5.2	26.1±5.3	28.4±4.7	29.0±5.7	<0.01	<0.01	<0.01	0.96
SBP [mmHg] (n=703)	150.8±21.5	146.3±19.0	156.1±22.6	145.6±20.2	<0.01	<0.01	1.00	<0.01
DBP [mmHg] (n=703)	91.7±13.3	90.4±11.9	94.1±13.3	87.6±14.7	<0.01	<0.01	0.16	<0.01
Known duration of HT (months) (n=612)	96 (42-179)	60 (24-112)	128 (60-205)	132 (60-228)	<0.01	<0.01	<0.01	1.00
Anti-HT medication (DDD)	3.0 (1.5-4.7)	2.0 (1.0-3.1)	4.0 (2.3-5.7)	2.9 (1.8-4.0)	<0.01	<0.01	0.01	<0.01
Plasma aldosterone (pmol/L) (n=703)	848 (555-1382)	877 (591-1437)	868.3 (566-1376)	690 (466-1368)	0.08	N.A.	N.A.	N.A.
DRC (mU/L) (n=300)	4.0 (2.0-8.0)	3.0 (1.5-4.9)	4.1 (2.9-9.2)	6.5 (3.5-14.2)	<0.01	0.01	<0.01	0.07
ARR_DRC (n=300)	213 (91-423)	297 (165-586)	224 (86-391)	236 (113-769)	<0.01	0.03	<0.01	0.10
PRA (pmol/L/min) (n=396)	3.8 (1.3-7.7)	2.6 (1.3-6.4)	3.8 (1.3-7.7)	5.8 (2.6-7.7)	0.02	0.49	0.01	0.14
ARR_PRA (n=396)	256 (116-648)	375 (126-807)	257 (116-625)	166 (90-346)	0.01	0.47	<0.01	0.06
Lowest serum K ⁺ (mmol/L) (n=622)	3.1 (2.7-3.4)	3.0 (2.6-3.4)	3.1 (2.8-3.5)	3.2 (2.9-3.5)	<0.01	0.01	0.01	1.00
Albuminuria (mg/day) (n=416)	10.0 (2.8-21.5)	10.0 (4.0-15.0)	10.2 (2.8-33.4)	7.1 (1.4-19.0)	0.18	N.A.	N.A.	N.A.
Creatinine (mmol/L) (n=620)	70.7 (60.0-84.0)	61.9 (53.0-74.3)	76.9 (63.6-88.4)	70.8 (61.9-94.0)	<0.01	<0.01	<0.01	1.00
eGFR (mL/min/1.73m ²) (n=503)	84.8 (70.3-95.7)	89.0 (78.9-100.0)	79.0 (66.3-92.5)	77.4 (61.6-93.6)	<0.01	<0.01	<0.01	1.00
LVH (n=455)	233 (51.2%)	61 (36.8%)	131 (61.5%)	41 (54.0%)	<0.01	<0.01	0.01	0.71
Diabetes (n=552)	84 (15.2%)	14 (7.0%)	48 (18.1%)	22 (25.3%)	<0.01	<0.01	<0.01	0.24
LI (n=675)	12.0 (6.3-26.2)	13.9 (6.7-30.0)	12.0 (6.3-25.7)	8.6 (5.4-17.2)	0.01	0.82	0.01	0.07
SL_RAV (n=604)	20.3 (5.5-33.8)	20.5 (6.8-33.3)	20.3 (5.7-35.0)	18.9 (4.7-33.5)	0.75	N.A.	N.A.	N.A.
SL_LAV (n=610)	14.0 (6.0-25.6)	12.9 (6.0-24.3)	14.5 (5.8-27.2)	14.8 (7.8-25.5)	0.39	N.A.	N.A.	N.A.
CLR (n=607)	0.3 (0.2-0.7)	0.3 (0.1-0.6)	0.3 (0.1-0.7)	0.4 (0.2-0.7)	0.06	N.A.	N.A.	N.A.
CL supp (n=607)	519 (85.5%)	195 (88.2%)	248 (85.8%)	76 (78.4%)	0.07	N.A.	N.A.	N.A.
ILR (n=524)	4.6 (2.6-8.7)	4.4 (2.6-8.4)	4.6 (2.7-8.3)	5.5 (2.7-12.2)	0.34	N.A.	N.A.	N.A.
Adrenal nodule (mm) (n=603)	13 (9-17)	15 (10-18)	12 (9-16)	11 (7-17)	<0.01	<0.01	<0.01	0.92
SBP [mmHg] – Follow-up (n=703)	128.8 ± 13.6	120.9 ± 9.5	132.0 ± 12.6	137.4 ± 15.8	<0.01	<0.01	<0.01	<0.01

VARIABLE	Total cohort	CLINICAL SUCCESS		Overall P-value	Pairwise Comparison – P values		
		Complete	Partial		C vs P	C vs M	P vs M
DBP [mmHg] – Follow-up (n=703)	81.3 ± 10.0	76.8 ± 7.3	83.0 ± 10.0	86.5 ± 11.0	<0.01	<0.01	<0.01
DDD – Follow-up	0.7 (0.0-2.5)	0.0 (0.0-0.0)	1.5 (0.5-3.0)	3.0 (1.5-4.9)	<0.01	<0.01	<0.01
Delta SBP (pre-post) [mmHg] (n=703)	22.0 ± 22.0	25.3 ± 19.8	24.1 ± 22.0	8.2 ± 22.1	<0.01	1.00	<0.01
Delta DBP (pre-post) [mmHg] (n=703)	10.5 ± 13.9	13.7 ± 11.9	11.1 ± 13.1	1.1 ± 16.5	<0.01	0.07	<0.01
Delta DDD (pre-post)	1.7 (0.5-3.0)	2.0 (1.0-3.1)	2.0 (1.0-3.4)	-1.5 (-0.8-1.0)	<0.01	1.00	<0.01
Delta SBP (pre-post) (%) (n=703)	13.3 ± 13.1	16.1 ± 11.7	14.1 ± 12.0	4.5 ± 15.1	<0.01	0.17	<0.01
Delta DBP (pre-post) (%) (n=703)	10.0 ± 14.8	14.0 ± 11.8	10.7 ± 12.6	1.3 ± 20.5	<0.01	0.02	<0.01
Delta DDD (pre-post) (%)	76.2 (37.1-100)	100 (100-100)	53.8 (33.5-77.8)	-17.2 (-83.2-33.3)	<0.01	<0.01	<0.01

All variables refer to baseline data unless otherwise stated. All quantitative and normally distributed variables are reported as mean ± standard deviation; non-normally distributed variables are presented as median with lower and upper quartiles in parenthesis. P-values <0.05 were considered statistically significant. Adrenal nodule refers to diameter of largest nodule at pathology. SBP/DBP/DDD-Follow-up refer to variable measured at 6-12 months; Delta SBP/DBP/DDD (pre-post) refer to the difference between pre-surgical and post-surgical blood pressure (SBP or DBP) or anti-hypertensive medication (DDD)

Table 3
Characteristics of patients with unilateral PA stratified for biochemical outcome.

VARIABLE	Total cohort	BIOCHEMICAL SUCCESS			Overall P-value	Pairwise Comparison – P values		
		Complete	Partial	Absent		C vs P	C vs M	P vs M
Biochemical Outcome	699	656 (93.9%)	27 (3.9%)	16 (2.3%)	N.A.	N.A.	N.A.	N.A.
Age (years)	50.8±10.9	50.8±10.9	51.8±9.9	48.7±12.5	0.72	N.A.	N.A.	N.A.
Female	308 (44.1%)	291 (44.4%)	12 (44.4%)	5 (31.3%)	0.58	N.A.	N.A.	N.A.
BMI (kg/m ²) (n=697)	27.6±5.2	27.6±5.2	25.6±5.3	30.0±6.6	0.04	0.14	0.24	0.03
SBP (mmHg) (n=697)	150.8±21.5	151.3±21.6	142.4±20.7	145.8±13.1	0.09	N.A.	N.A.	N.A.
DBP (mmHg) (n=697)	91.8±13.3	92.0±13.3	86.7±14.5	91.5±10.6	0.33	N.A.	N.A.	N.A.
Known duration of HT (months) (n=606)	96 (39-177)	96 (36-168)	120 (63-188)	152 (42-241)	0.19	N.A.	N.A.	N.A.
Anti-HT medication (DDD)	3.0 (1.5-4.7)	3.0 (1.5-4.7)	3.0 (2.0-3.5)	4.0 (2.0-5.4)	0.48	N.A.	N.A.	N.A.
Plasma aldosterone (pmol/L) (n=697)	858 (558-1382)	860 (566-1393)	768 (580-1617)	518 (333-901)	0.01	1.00	0.01	0.04
DRC (mU/L) (n=294)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	11.5 (6.1-14.9)	6.1 (3.2-14.0)	0.19	N.A.	N.A.	N.A.
ARR_DRC (n=294)	210 (89-414)	216 (93-423)	64 (37-154)	110 (59-277)	0.08	N.A.	N.A.	N.A.
PRA (pmol/L/min) (n=396)	3.8 (1.3-7.7)	3.8 (1.3-7.7)	2.6 (1.3-5.1)	5.8 (3.8-7.7)	0.45	N.A.	N.A.	N.A.
ARR_PRA (n=396)	256 (116-648)	267 (117-643)	236 (112-876)	79 (43-129)	0.05	N.A.	N.A.	N.A.
Lowest serum K ⁺ (mmol/L) (n=616)	3.1 (2.7-3.5)	3.1 (2.7-3.4)	3.3 (3.0-3.6)	3.0 (2.6-3.4)	0.11	N.A.	N.A.	N.A.
Albuminuria (mg/day) (n=410)	10.0 (2.8-21.5)	10.0 (2.7-21.1)	10.2 (5.3-24.5)	6.1 (4.5-14.0)	0.75	N.A.	N.A.	N.A.
Creatinine [mmol/L] (n=614)	70.7 (60.0-84.0)	70.7 (60.0-85.3)	61.9 (53.0-70.7)	70.7 (65.4-85.7)	0.01	0.01	1.00	0.07
eGFR (mL/min/1.73m ²) (n=497)	84.8 (70.3-95.7)	84.5 (70.1-95.3)	87.3 (76.8-95.0)	88.8 (55.0-103.6)	0.49	N.A.	N.A.	N.A.
LVH (n=449)	233 (51.2%)	221 (51.6%)	8 (44.4%)	4 (44.4%)	0.78	N.A.	N.A.	N.A.
Diabetes (n=546)	84 (15.2%)	78 (15.1%)	3 (12.0%)	3 (27.3%)	0.50	N.A.	N.A.	N.A.
LI (n=669)	11.9 (6.3-26.1)	12.4 (6.5-27.1)	6.5 (3.1-11.3)	5.7 (4.4-10.0)	<0.01	<0.01	0.01	1.00
SL_RAV (n=598)	20.3 (5.5-33.8)	20.3 (5.7-34.2)	20.5 (3.6-28.6)	16.6 (3.2-32.0)	0.47	N.A.	N.A.	N.A.
SL_LAV (n=604)	14.0 (6.0-25.6)	14.0 (6.1-25.5)	13.1 (5.2-26.8)	14.2 (4.1-23.2)	0.96	N.A.	N.A.	N.A.
CLR (n=601)	0.3 (0.2-0.7)	0.3 (0.2-0.6)	0.6(0.3-1.2)	0.6(0.2-2.5)	<0.01	0.01	0.18	1.00
CL supp (n=601)	519(85.5%)	494 (86.7%)	18 (72.0%)	7(58.3%)	<0.01	0.43	0.01	0.25
ILR (n=518)	4.6 (2.6-8.7)	4.6(2.6-8.7)	5.3(2.9-7.3)	6.4 (2.5-19.9)	0.86	N.A.	N.A.	N.A.
Adrenal nodule (n=597)	13 (9-17)	13 (10-17)	8 (7-15)	14 (7-19)	0.02	0.01	1.00	0.23
SBP [mmHg] – Follow-up (n=697)	128.7 ± 13.7	128.4 ± 13.5	132.9 ± 16.6	136.2 ± 12.9	0.02	0.27	0.07	1.00

VARIABLE	Total cohort	BIOCHEMICAL SUCCESS		Absent	Overall P-value	Pairwise Comparison – P values		
		Complete	Partial			C vs P	C vs M	P vs M
DBP [mmHg] – Follow-up (n=697)	81.2 ± 10.0	81.0 ± 9.8	84.0 ± 13.1	86.9 ± 8.1	0.02	0.36	0.06	1.00
DDD – Follow-up	0.6 (0.0-2.5)	0.5 (0.0-2.5)	1.0 (0.3-2.0)	2.2 (1.0-4.2)	<0.01	0.43	<0.01	0.28
Delta SBP (pre-post) (mmHg) (n=697)	22.1 ± 22.0	22.9 ± 22.0	9.5 ± 20.9	9.7 ± 17.1	<0.01	0.01	0.05	1.00
Delta DBP (pre-post) (mmHg) (n=697)	10.5 ± 13.9	11.0 ± 13.8	2.6 ± 17.5	4.7 ± 9.5	<0.01	0.01	0.22	1.00
Delta DDD (pre-post)	1.6 (0.5-3.0)	1.7 (0.5-3.0)	1.5 (0.5-2.3)	0.8 (-0.7-4.4)	0.27	N.A.	N.A.	N.A.
Delta SBP (pre-post) (%) (n=697)	13.3 ± 13.1	13.8 ± 12.9	5.5 ± 13.6	6.0 ± 11.4	<0.01	<0.01	0.05	1.00
Delta DBP (pre-post) (%) (n=697)	10.0 ± 14.8	10.6 ± 14.2	0.4 ± 24.3	4.4 ± 10.3	<0.01	<0.01	0.29	1.00
Delta DDD (pre-post) (%)	76.7 (36.7-100.0)	82.2 (40.0-100.0)	50.0 (33.3-90.0)	27.4 (-50.1-70.9)	<0.01	0.12	<0.01	0.40

All variables refer to baseline data unless otherwise stated. All quantitative and normally distributed variables are reported as mean ± standard deviation; non-normally distributed variables are presented as median with lower and upper quartiles in parenthesis. P-values <0.05 were considered statistically significant. Adrenal nodule refers to diameter of largest nodule at pathology.

Table 4
Baseline correlates of clinical and biochemical outcome following adrenalectomy for unilateral PA

(A) Complete <i>versus</i> Partial + Absent					
CLINICAL OUTCOME			BIOCHEMICAL OUTCOME		
Variable	Unadjusted Analysis Odds Ratio (95% CI)	Adjusted Analysis P value Odds Ratio (95% CI)	Unadjusted Analysis Odds Ratio (95% CI)	Adjusted Analysis P value Odds Ratio (95% CI)	P value
Age (years)	0.94 (0.92-0.95)	<0.01 0.95 (0.93-0.98)	1.00 (0.97-1.03)	0.91 0.98 (0.94-1.02)	0.32
Lowest serum K ⁺ (mmol/L)	1.64 (1.22-2.21)	<0.01 1.43 (0.95-2.15)	1.56 (0.86-2.88)	0.15 1.43 (0.69-2.95)	0.34
Anti-HT medication (DDD)	0.68 (0.62-0.75)	<0.01 0.80 (0.70-0.90)	0.96 (0.85-1.09)	0.48 0.87 (0.74-1.02)	0.09
eGFR (mL/min/1.73m ²)	1.02 (1.01-1.03)	<0.01 1.01 (1.00-1.02)	0.99 (0.98-1.01)	0.37 0.99 (0.97-1.01)	0.17
SBP (mmHg)	0.98 (0.98-0.99)	<0.01 0.99 (0.98-1.01)	1.02 (1.00-1.04)	0.02 1.03 (1.01-1.05)	0.01
BMI (kg/m ²)	0.90 (0.87-0.93)	<0.01 0.98 (0.94-1.03)	1.02 (0.96-1.08)	0.62 0.95 (0.88-1.02)	0.15
Sex (ref. female)	4.37 (3.16-6.07)	<0.01 2.25 (1.40-3.62)	1.22 (0.65-2.33)	0.54 0.99 (0.42-2.32)	0.98
LVH (ref. not detected)	2.53 (1.71-3.76)	<0.01 1.61 (1.01-2.59)	0.75 (0.34-1.64)	0.47 0.70 (0.30-1.62)	0.40
(B) Complete + Partial <i>versus</i> Absent					
CLINICAL OUTCOME			BIOCHEMICAL OUTCOME		
Variable	Unadjusted Analysis Odds Ratio (95% CI)	Adjusted Analysis P value Odds Ratio (95% CI)	Unadjusted Analysis Odds Ratio (95% CI)	Adjusted Analysis P value Odds Ratio (95% CI)	P value
Age (years)	0.96 (0.94-0.98)	<0.01 0.95 (0.92-0.98)	1.02 (0.97-1.06)	0.43 1.03 (0.96-1.11)	0.52
Lowest serum K ⁺ (mmol/L)	1.53 (1.03-2.29)	0.04 1.18 (0.70-2.00)	0.92 (0.35-2.51)	0.87 0.90 (0.26-3.12)	0.87
Anti-HT medication (DDD)	1.08 (0.99-1.19)	0.09 1.27 (1.08-1.50)	0.88 (0.75-1.07)	0.17 0.79 (0.61-1.01)	0.06
eGFR (mL/min/1.73m ²)	1.01 (1.00-1.03)	0.02 1.01 (1.00-1.02)	1.01 (0.98-1.04)	0.55 1.01 (0.97-1.04)	0.72
SBP (mmHg)	1.01 (1.00-1.03)	0.01 1.03 (1.01-1.04)	1.01 (0.99-1.04)	0.35 1.03 (0.99-1.07)	0.14
BMI (kg/m ²)	0.95 (0.91-0.98)	<0.01 0.90 (0.85-0.96)	0.93 (0.85-1.01)	0.07 0.89 (0.79-1.00)	0.04
Sex (ref. female)	3.06 (1.94-4.97)	<0.01 2.89 (1.49-5.59)	1.75 (0.63-5.62)	0.30 1.91 (0.41-8.99)	0.41
LVH (ref. not detected)	1.14 (0.70-1.88)	0.60 1.39 (0.76-2.54)	0.76 (0.19-2.90)	0.68 0.54 (0.12-2.37)	0.42
(C) Complete <i>versus</i> Absent					
CLINICAL OUTCOME			BIOCHEMICAL OUTCOME		

Variable	Unadjusted Analysis		Adjusted Analysis		Unadjusted Analysis		Adjusted Analysis		Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	0.93 (0.90-0.95)	<0.01	0.92 (0.88-0.96)	<0.01	1.02 (0.97-1.06)	0.44	1.02 (0.95-1.10)	0.55				
Lowest serum K ⁺ (mmol/L)	1.94 (1.26-3.03)	<0.01	1.24 (0.64-2.39)	0.52	0.95 (0.36-2.58)	0.92	0.98 (0.28-3.47)	0.97				
Anti-HT medication (DDD)	0.83 (0.74-0.94)	<0.01	1.05 (0.86-1.28)	0.61	0.88 (0.75-1.07)	0.18	0.78 (0.61-1.00)	0.05				
eGFR (mL/min/1.73m ²)	1.03 (1.02-1.05)	<0.01	1.01 (0.99-1.03)	0.18	1.01 (0.98-1.04)	0.58	1.00 (0.97-1.04)	0.82				
SBP (mmHg)	1.00 (0.99-1.01)	0.77	1.02 (1.00-1.04)	0.08	1.01 (0.99-1.04)	0.32	1.03 (0.99-1.07)	0.14				
BMI (kg/m ²)	0.91 (0.87-0.95)	<0.01	0.91 (0.85-0.97)	<0.01	0.93 (0.85-1.01)	0.08	0.88 (0.79-0.99)	0.04				
Sex (ref. female)	6.54 (3.98-11.04)	<0.01	4.48 (2.10-9.60)	<0.01	1.75 (0.63-5.62)	0.30	1.90 (0.40-8.97)	0.42				
LVEH (ref. not detected)	2.02 (1.17-3.51)	0.01	1.89 (0.90-3.99)	0.09	0.75 (0.18-2.87)	0.67	0.54 (0.12-2.34)	0.41				

Logistic regression analyses were performed at the patient level to identify correlates of clinical and biochemical outcome. Eight covariates were entered into each model and their unadjusted odds ratios are shown with the corresponding odds ratio adjusted for the confounding effects of the other covariates in the model. The final adjusted models included data from 414 patients with complete data for all 8 variables (clinical outcome: complete, n=158; partial, n=192; absent, n=64 patients; biochemical outcome: complete, n=387; partial, n=18; absent, n=9 patients). Odds ratios are shown with 95% confidence intervals (CI) in parenthesis.