

# Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort

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## Summary

**Background** Although unilateral primary aldosteronism is the most common surgically correctable cause of hypertension, no standard criteria exist to classify surgical outcomes. We aimed to create consensus criteria for clinical and biochemical outcomes and follow-up of adrenalectomy for unilateral primary aldosteronism and apply these criteria to an international cohort to analyse the frequency of remission and identify preoperative determinants of successful outcome.

**Methods** The Primary Aldosteronism Surgical Outcome (PASO) study was an international project to develop consensus criteria for outcomes and follow-up of adrenalectomy for unilateral primary aldosteronism. An international panel of 31 experts from 28 centres, including six endocrine surgeons, used the Delphi method to reach consensus. We then retrospectively analysed follow-up data from prospective cohorts for outcome assessment of patients diagnosed with unilateral primary aldosteronism by adrenal venous sampling who had undergone a total adrenalectomy, consecutively included from 12 referral centres in nine countries. On the basis of standardised criteria, we determined the proportions of patients achieving complete, partial, or absent clinical and biochemical success in accordance with the consensus. We then used logistic regression analyses to identify preoperative factors associated with clinical and biochemical outcomes.

**Findings** Consensus was reached for criteria for six outcomes (complete, partial, and absent success of clinical and biochemical outcomes) based on blood pressure, use of antihypertensive drugs, plasma potassium and aldosterone concentrations, and plasma renin concentrations or activities. Consensus was also reached for two recommendations for the timing of follow-up assessment. For the international cohort analysis, we analysed clinical data from 705 patients recruited between 1994 and 2015, of whom 699 also had biochemical data. Complete clinical success was achieved in 259 (37%) of 705 patients, with a wide variance (range 17–62), and partial clinical success in an additional 334 (47%, range 35–66); complete biochemical success was seen in 656 (94%, 83–100) of 699 patients. Female patients had a higher likelihood of complete clinical success (odds ratio [OR] 2.25, 95% CI 1.40–3.62;  $p=0.001$ ) and clinical benefit (complete plus partial clinical success; OR 2.89, 1.49–5.59;  $p=0.002$ ) than male patients. Younger patients had a higher likelihood of complete clinical success (OR 0.95 per extra year, 0.93–0.98;  $p<0.001$ ) and clinical benefit (OR 0.95 per extra year, 0.92–0.98;  $p=0.004$ ). Higher levels of preoperative medication were associated with lower levels of complete clinical success (OR 0.80 per unit increase, 0.70–0.90;  $p<0.001$ ).

**Interpretation** These standardised outcome criteria are relevant for the assessment of the success of surgical treatment in individual patients and will allow the comparison of outcome data in future studies. The variable baseline clinical characteristics of our international cohort contributed to wide variation in clinical outcomes. Most patients derive clinical benefit from adrenalectomy, with younger patients and female patients more likely to have a favourable surgical outcome. Screening for primary aldosteronism should nonetheless be done in every individual fulfilling US Endocrine Society guideline criteria because biochemical success without clinical success is by itself clinically important and older women and men can also derive post-operative clinical benefit.

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## Introduction

Primary aldosteronism is a form of endocrine hypertension characterised by inappropriately high plasma aldosterone concentrations relative to suppressed

plasma renin.<sup>1</sup> The prevalence of primary aldosteronism is reported as 5% in the general hypertensive population,<sup>2</sup> increasing to 10% in referred populations and 15–20% in patients with treatment-resistant hypertension,<sup>3</sup>



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\*A complete list of PASO study investigators is provided in the appendix

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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. Proportions of patients with biochemical remission are high across various reports (96–100%); by contrast, clinical remission has been reported for a much wider range (20–72%) of patients. This variability might be real, across centres, or might reflect the absence of standardised criteria and differences in post-surgical follow-up. We noted 18 studies, published between 1998 and 2015, in which total adrenalectomy was used to treat unilateral primary aldosteronism; these studies used different outcome criteria that varied from normalisation of plasma potassium concentrations with normalisation or improvement of blood pressure to criteria that also took into account the use of antihypertensive drugs and plasma aldosterone and renin concentrations or plasma renin activities. These studies rarely separated biochemical criteria (plasma potassium, renin, and aldosterone measurements) from clinical criteria (blood pressure measurements and use of antihypertensive drugs). The assessment of biochemical success of adrenalectomy separately from clinical success is important because a patient with primary aldosteronism can be correctly biochemically diagnosed and successfully treated, but maintain background primary hypertension after successful adrenalectomy.

### Added value of this study

The Primary Aldosteronism Surgery Outcome (PASO) study consisted of two parts. First, using the Delphi method, we were able to reach consensus for criteria for six outcomes (complete, partial, and absent success of clinical and biochemical outcomes) for unilateral adrenalectomy and two recommendations for the time and interval of follow-up. In an international multicentre study, we applied these criteria in a retrospective analysis of a large prospective cohort of patients who had undergone adrenalectomy. Proportions of patients with complete clinical success ranged from 17% to 62%; complete biochemical success averaged 94%. Female sex and younger age were independently associated with clinical success.

### Implications of all the available evidence

This study establishes a standard set of outcome criteria for the surgical treatment of unilateral primary aldosteronism. The criteria are relevant for the assessment of the success of surgical treatment in individual patients and for the comparison of outcome data in studies. We identified that younger patients and female patients are more likely to have a favourable surgical outcome. These data will be useful for health-care professionals counselling patients with unilateral primary aldosteronism prior to adrenalectomy about the expected post-operative clinical benefit.

although estimates vary widely.<sup>4</sup> Several studies have shown a higher prevalence of cardiovascular and cerebrovascular morbidity and mortality in patients with primary aldosteronism than in patients with primary hypertension matched for age, sex, and blood pressure,<sup>5–8</sup> with resolution of excess risk after surgical or specific medical treatment.<sup>9–10</sup> As such, early diagnosis and appropriate treatment of primary aldosteronism are essential to minimise the increased risk associated with this disorder.

Primary aldosteronism is classified into unilateral and bilateral forms of the disease, which must be distinguished because, although the unilateral form can respond well to adrenalectomy, the bilateral form is treated with mineralocorticoid receptor antagonists.<sup>11</sup> Although adrenal venous sampling is the recommended procedure to distinguish primary aldosteronism subtypes,<sup>11</sup> it is not widely available, with some centres relying on CT or MRI for determination of lateralisation.

Surgical treatment of unilateral primary aldosteronism should resolve the excessive aldosterone secretion in all patients. Persistence of primary aldosteronism after adrenalectomy suggests that the initial diagnosis was incorrect, with the patient having bilateral rather than unilateral primary aldosteronism. To define post-surgical outcomes, specific clinical and biochemical criteria are needed for persistent or recurrent disease. Reported proportions of patients achieving clinical

remission vary widely between centres (16–72%); this variation is attributed to several underlying factors such as background primary hypertension, age, longstanding primary aldosteronism, advanced renal failure, or other comorbidities.<sup>12–15</sup> However, heterogeneity might also reflect the absence of standardised criteria to classify outcomes of adrenalectomy for unilateral primary aldosteronism. As such, we hypothesised that standardised uniform outcome criteria applied across a large multicentre patient cohort might minimise the previously reported variation in outcome results. Such uniform criteria might not only improve clinical care of patients with primary aldosteronism, but could also provide a basis for comparison of outcome data from different clinical centres.

The objectives of the Primary Aldosteronism Surgical Outcome (PASO) study were to establish an international consensus for a set of standardised criteria for clinical and biochemical outcomes of adrenalectomy for unilateral primary aldosteronism; to apply these criteria to follow-up data in a large multicentre cohort of patients with primary aldosteronism from different clinical expert centres to calculate the proportion of patients achieving remission; to identify the preoperative determinants of successful outcome; and to determine the extent to which these outcome determinants might account for differing proportions of patients achieving complete success between centres.

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