

# Outcomes of Drug-Based and Surgical Treatments for Primary Aldosteronism



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**Treatments for primary aldosteronism (PA) aim to correct or prevent the deleterious consequences of hyperaldosteronism: hypertension, hypokalemia, and direct target organ damage. Patients with unilateral PA considered fit for surgery can undergo laparoscopic adrenalectomy, which significantly decreases blood pressure (BP) and medications in most cases and cures hypertension in about 40%. Mineralocorticoid receptor antagonists (MRA) are used to treat patients with bilateral PA and those with unilateral PA if surgery is not possible or not desired. Spironolactone is more potent than eplerenone, but high doses are poorly tolerated in men. MRA can be replaced or complemented with epithelial sodium channel blockers, such as amiloride. Thiazide diuretics and calcium channel blockers are used when the first-line drugs are insufficient to control BP. Dietary sodium restriction should be implemented in all cases because the deleterious consequences of hyperaldosteronism are dependent on salt loading. Several studies comparing the results of surgery and MRA have reported no differences in terms of BP, serum potassium concentration, or cardiovascular and kidney outcomes, although the benefits of treatment tend to be observed sooner with surgery. Patients with PA display relative glomerular hyperfiltration, which is reversed by specific treatment, revealing CKD in 30% of patients. However, further kidney damage is lessened by the treatment of PA.**

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**Key Words:** Hyperaldosteronism, Adrenalectomy, Mineralocorticoid receptor antagonists, Epithelial sodium channel blockers, Chronic kidney disease

## INTRODUCTION

Primary aldosteronism (PA) is the state of autonomous aldosterone overproduction by one or both adrenal glands.<sup>1</sup> Activation of the mineralocorticoid receptor increases the number of epithelial sodium channels (ENaCs) and sodium chloride cotransporters on the epithelial cell membrane of distal and collecting tubules.<sup>2</sup> This leads to sodium reabsorption and potassium secretion, resulting in an increase in plasma volume and hypokalemia. However, sodium availability in the distal nephron, which depends on salt loading, must exceed a certain amount for these consequences to occur. Hypertension results partly from an increase in plasma volume and partly from the aldosterone-mediated vasoconstriction of systemic arteries.<sup>3</sup> Target organ damage is mostly because of hypertension, but aldosterone also promotes oxidative stress, inflammation, and fibrosis in the kidney and other organs (heart, vessels, and adipose tissue). These effects are also

dependent on salt loading and may be partly independent of the mineralocorticoid receptor.<sup>4-6</sup>

Treatment aims to decrease the morbidity and mortality associated with PA and to improve the quality of life of patients. Economic constraints make it necessary to achieve these ends at the lowest possible cost. The most logical way to achieve these goals is to normalize aldosterone secretion. This is possible in patients with unilateral PA through removal of the offending adrenal gland. Aldosterone synthase inhibitors are currently being developed but are not yet used in clinical practice.

Mineralocorticoid receptor antagonists (MRAs) counteract most but not all the biologic effects of hyperaldosteronism. However, they yield clinical results comparable with those achieved by adrenalectomy. ENaC blockers impede only some of the many pathways leading to target organ damage but are useful adjunctive treatments, together with dietary sodium restriction, for controlling blood pressure (BP) and hypokalemia. Nonspecific antihypertensive agents are often required in addition to these specific treatments to control hypertension.

We will begin by describing the principal treatments for PA—surgery and antihypertensive drugs—and reviewing their outcomes. We will then discuss the most appropriate uses of these treatments according to PA subtype and the clinical circumstances and individual preferences of patients.

## UNILATERAL ADRENALECTOMY

The vast majority of adrenal lesions causing unilateral PA are small and benign and are, therefore, ideal candidates for laparoscopic adrenalectomy, for which morbidity is lower and hospital stays are shorter than for open surgery.<sup>7,8</sup> Several surgeons have advocated partial adrenalectomy as a safe and feasible way of removing single aldosterone-producing adenomas (APA).<sup>9,10</sup> However, the benefits of this adrenal gland-sparing approach are questionable in

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PA because contralateral tumors requiring subsequent adrenalectomy are very rare. Moreover, 10% to 25% of patients with unilateral PA have multiple adjacent nodules that may be missed on preoperative adrenal imaging, and the largest lesion is not necessarily the lesion responsible for PA.<sup>11</sup> Several percutaneous alternatives for the destruction of APAs have been proposed, including ethanol injection, arterial embolization, cryoablation, and radiofrequency ablation.<sup>11,12</sup> These techniques are less invasive than surgery, but the long-term outcome and risks are uncertain. They should, therefore, be used only within the confines of a study protocol.

Surgeons may opt for a transperitoneal or for a retroperitoneal approach. Both approaches have drawbacks and advantages. The lateral transperitoneal laparoscopic approach exposes the adrenal gland to a greater extent, whereas the retroperitoneal approach avoids facing adhesions in patients who have previously undergone intra-abdominal surgery and potentially reduces the duration of the patient's stay in hospital.<sup>13</sup> Laparoscopic adrenalectomy usually requires 3 to 4 ports for the introduction of the instruments, but a single-port transumbilical approach is possible.<sup>14,15</sup> Robot-assisted laparoscopic adrenalectomy is feasible and safe but more expensive, and its advantages over conventional laparoscopy have yet to be definitively demonstrated.<sup>15-17</sup>

The mean operating time for laparoscopic adrenalectomy performed by experienced surgeons in major series is between 1 and 2 hours, and mean hospital stay is about 3 days.<sup>18,19</sup> Conversion to open surgery is required in less than 5% of cases.<sup>8</sup> Perioperative mortality is less than 0.5%, nonfatal complications occur in 5% to 15% of cases, and most of them are benign (temporary relaxation and/or hypoesthesia of the abdominal wall).<sup>7,8,18</sup> Fewer than 2% of patients experience severe complications: hemorrhage requiring transfusion and cardiac or respiratory destabilization.<sup>7,8,18</sup> However, cases of major complications have been reported outside referral centers.<sup>20</sup> Surgery should be performed by an experienced surgeon at an institution with a high volume of such interventions. In such settings, outpatient laparoscopic adrenalectomy is possible in selected cases: patients younger than 65 years, tumors of less than 6 cm in diameter, no significant cardiorespiratory disease, first case of the day to be managed in the surgical program, residence less than 30 minutes from the hospital by car, and treatment with no more than 3 antihypertensive agents.<sup>21-23</sup>

Patients should be treated with an MRA and potassium supplements to lower BP and to correct hypokalemia before surgery. Preoperative mineralocorticoid receptor

blockade for a few weeks before surgery may also decrease the risk of postoperative hypoaldosteronism because of the chronic suppression of aldosterone secretion in the contralateral gland. Nonetheless, postoperative hyperkalemia is seen in up to 30% of patients.<sup>24,25</sup> It is usually mild and transient, but MRA treatment and potassium supplements should be discontinued at the time of surgery to minimize the risk, and serum potassium concentrations should be monitored closely, particularly in patients with CKD.<sup>25</sup> In addition to the restriction of potassium-rich food, fludrocortisone has been used in rare cases of persistent hyperkalemia because of postoperative hypoaldosteronism.<sup>24</sup> Hormonal studies should be carried out for patients with high BP after surgery, to distinguish between persistent PA and associated essential hypertension.

### OUTCOMES OF ADRENALECTOMY IN UNILATERAL PA

We discuss here the findings of a systematic review of large surgical series published since 2000.<sup>11</sup> This time limit was

set to correspond to current outcomes of laparoscopic surgery in patients with unilateral PA diagnosed with current protocols. This evidence base is nonetheless limited by the lack of comparison with drug-based treatment and medium-term evaluations of mostly intermediate outcomes (BP, serum potassium, and subclinical target organ damage).

By definition, unilateral adrenalectomy should normalize aldosterone secretion in all cases of unilateral PA. However, 5% to 10% of patients display residual autonomous aldosterone

production after surgery, even if hypertension is cured,<sup>26</sup> and if adrenal venous sampling (AVS) was used in the diagnostic evaluation. Hypokalemia, when present, resolves in more than 95% of cases, in all series. The mean rate of hypertension cure is 40%, with a high variability between series. Patients with persistent hypertension nonetheless experience a clinically significant decline in BP (of between 20 and 40 mm Hg for systolic BP) and a decrease in the number of antihypertensive drug classes used (1 or 2 fewer classes). Less than 25% of patients experience no apparent BP benefit from surgery.

An increase in markers of oxidative stress is observed more frequently in patients with PA than in patients with essential hypertension, and the levels of these markers decrease significantly after adrenalectomy in patients with unilateral disease.<sup>27</sup>

Patients with PA have higher cardiovascular morbidity and greater subclinical organ damage than expected on the basis of their BP.<sup>28</sup> Many studies have shown that

#### CLINICAL SUMMARY

- The goals of treatment are the normalization of serum potassium concentration, blood pressure (BP) control, and prevention of the direct effects of excess aldosterone on target organs.
- The nonsurgical treatment of PA is based on mineralocorticoid receptor antagonists and dietary sodium restriction.
- Epithelial sodium channel blockers are used when mineralocorticoid receptor antagonists are not well tolerated; thiazide diuretics and calcium channel blockers are used when BP control is insufficient with the first-line treatment.
- Laparoscopic adrenalectomy is safe and decreases BP and medication requirements in patients with unilateral PA; drug-based treatments are appropriate in cases in which surgery is inappropriate or not desired.

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