MANAGEMENT OF ENDOCRINE DISEASE

# The role of surgical adrenalectomy in primary aldosteronism

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## Abstract

Primary aldosteronism is common and contributes to adverse cardiovascular, kidney, and metabolic outcomes. When instituted early and effectively, targeted therapies can mitigate these adverse outcomes. Surgical adrenalectomy is among the most effective treatments because it has the potential to cure, or attenuate the severity of, pathologic aldosterone excess, resulting in a host of biochemical and clinical changes that improve health outcomes. Herein, we review the role of surgical adrenalectomy in primary aldosteronism while emphasizing the physiologic ramifications of surgical intervention, and compare these to other targeted medical therapies for primary aldosteronism. We specifically review the role of curative adrenalectomy for unilateral primary aldosteronism, the role of non-curative adrenalectomy for bilateral primary aldosteronism, and how these interventions influence biochemical and clinical outcomes in relation to medical therapies for primary aldosteronism.

*European Journal of Endocrinology*
(2020) **183**, R185–R196

European Journal of Endocrinology

## Introduction

Primary aldosteronism is common and largely unrecognized (1, 2, 3, 4, 5, 6, 7, 8). It is likely that future studies will continue to demonstrate in greater detail the highly underestimated prevalence of primary aldosteronism. The public health relevance of these facts is that primary aldosteronism accelerates the pathogenesis of cardiovascular, kidney, and metabolic diseases, but when adequately treated, these risks can largely be mitigated.

Although there are several targeted treatments for primary aldosteronism, the definitive treatment is curative surgical adrenalectomy; the greatest clinical benefits and biochemical improvements are achieved by eradicating the source of aldosterone excess. Although there are no robust randomized controlled trials to validate the efficacy of surgical adrenalectomy, observational studies have consistently shown that adrenalectomy to cure or

**Invited Author's profile**

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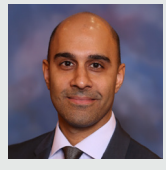

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-0863

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attenuate the severity of disease is associated with superior outcomes. Herein, we review the adverse consequences of primary aldosteronism that justify targeted treatment, and we review the efficacy of curative and non-curative adrenalectomy in comparison to medical therapies such as mineralocorticoid receptor (MR) antagonists and dietary sodium restriction.

## Adverse health outcomes in primary aldosteronism

Without targeted treatment to abolish, lower, or block aldosterone, primary aldosteronism leads to disproportionately high rates of cardiometabolic disease. Although there are no robust, prospective, and randomized trials that have confirmed that the deleterious effects of aldosterone are modifiable beyond its effects on blood pressure, several large observational human studies have provided convincing evidence to suggest that when compared to patients with essential hypertension, patients with untreated primary aldosteronism have a higher risk for coronary artery disease (9, 10, 11, 12, 13, 14, 15, 16, 17, 18), congestive heart failure (11, 12, 13, 14, 15, 17, 19, 20), left ventricular hypertrophy (19, 20, 21, 22), atrial fibrillation (9, 10, 11, 12, 13, 14, 17, 20, 23, 24), stroke (9, 10, 11, 12, 14, 15, 17), diabetes mellitus (11, 17, 25, 26, 27, 28), metabolic syndrome (26, 29), decreased bone density (30, 31, 32, 33), and kidney disease (34, 35, 36, 37, 38, 39, 40, 41). Importantly, many of these observational studies demonstrated that the increased cardiometabolic risk associated with untreated primary aldosteronism, when compared to essential hypertension, persists even when patients are matched for blood pressure. Therefore, the current consensus is that primary aldosteronism increases the risk for adverse cardiometabolic outcomes independent of blood pressure; an observation that has also been made in basic and animal experiments (42, 43, 44).

A meta-analysis by Monticone *et al*. consolidated many of these observational studies to provide a comprehensive assessment of risk in primary aldosteronism (45). The authors included 31 studies to compare 3838 patients with untreated primary aldosteronism with 9284 patients with essential hypertension over a median follow-up time of 8.8 years from the diagnosis of hypertension. They found that compared with essential hypertension, patients with untreated primary aldosteronism had an increased risk of coronary artery disease (odds ratio (OR) 1.77 (95% CI 1.10, 2.83)), congestive heart failure (OR 2.05 (95% CI 1.11, 3.78)), left ventricular hypertrophy (OR 2.29 (95% CI 1.65, 3.17)), atrial fibrillation (OR 3.52 (95% CI 2.06, 5.99)), stroke (OR 2.58 (95% CI 1.93, 3.45)), diabetes mellitus (OR 1.33 (95% CI 1.01, 1.74)), and metabolic syndrome (OR 1.53 (95% CI 1.22, 1.91)). These increased cardiometabolic risks persisted when only using studies where patients with untreated primary aldosteronism were matched by blood pressure to patients with essential hypertension (45).

Due to this disproportionately high cardiometabolic risk inherent to untreated primary aldosteronism, early diagnosis and targeted therapy are critical in order to reduce morbidity and mortality. The longstanding dogma for targeted therapy for primary aldosteronism has been to pursue curative adrenalectomy for unilateral primary aldosteronism and to prescribe lifelong MR antagonist therapy for bilateral primary aldosteronism (2). It should be noted, that in addition to resolving aldosterone excess, surgical adrenalectomy for primary aldosteronism has the additional advantage of potentially resolving the cortisol excess that is now recognized as a prevalent, and potentially clinically relevant, risk factor (27, 46, 47, 48, 49). Below, we discuss the indications and ramifications of surgical adrenalectomy for unilateral, and bilateral, primary aldosteronism, and how these compare to medical therapy.

## Biochemical sequelae of curative adrenalectomy for unilateral primary aldosteronism

For unilateral primary aldosteronism, the longstanding dogma echoed in expert guidelines recommends curative unilateral laparoscopic adrenalectomy as the treatment of choice for patients healthy enough, and willing, to undergo the procedure (2). The goal of adrenalectomy in unilateral primary aldosteronism is to cure the disease by completely removing the unilateral source of inappropriate aldosterone production, ideally identified via adrenal venous sampling.

The definition of surgical cure has recently been defined by the Primary Aldosteronism Surgery Outcomes (PASO) study. The PASO study set out to create standardized criteria by which to define post-adrenalectomy cure of unilateral primary aldosteronism (50). The PASO investigators devised definitions for both clinical and biochemical success using data from approximately 700 patients with unilateral primary aldosteronism. 'Complete clinical success' was defined as post-operative normalization of





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blood pressure without the use of any anti-hypertensive medication use. 'Complete biochemical success' was defined by normalization of serum potassium (if present pre-adrenalectomy) without the need for supplements, along with a decrease in circulating aldosterone and/or an increase in renin such that there was normalization of the aldosterone-to-renin ratio. Notably, there was a stark contrast in success rates between clinical and biochemical criteria. Whereas only 37% of patients met the criteria for complete clinical success, the vast majority of patients (94%) met the criteria for complete biochemical success (50). This discrepancy between clinical and biochemical success rates reflects the fact that most patients with unilateral primary aldosteronism will continue to have some degree of hypertension (though typically to a milder degree) (51, 52) following adrenalectomy even when biochemical success is achieved. This likely relates to the long-term vasculopathy induced by prolonged exposure to hypertension and pathologic aldosterone-MR interactions. This discrepancy is particularly prevalent among those with a more longstanding history of hypertension and the elderly (53).

The biochemical sequelae of adrenalectomy for unilateral primary aldosteronism seen in the PASO study (normalization of serum potassium, decrease in aldosterone, increase in renin, and decrease in the aldosterone-to-renin ratio) (50) mirror the results of prior studies (52, 54, 55, 56, 57, 58, 59, 60, 61, 62). These biochemical outcomes reflect the physiologic changes to be expected following complete removal of the source of inappropriate and excessive aldosterone production. Untreated primary aldosteronism is characterized by excessive MR activation which results in increased epithelial sodium channel (ENaC)-mediated sodium reabsorption, and a vicious cycle of intra-vascular volume expansion and glomerular hyperfiltration, and consequent increases in distal nephron sodium delivery and urinary excretion of potassium and hydrogen ions (7, 63, 64). When curative adrenalectomy is performed, aldosterone levels decline, MR activation decreases, ENaC-mediated sodium reabsorption is reduced, intravascular volume contracts or normalizes to induce a rise in renin and a decrease in the aldosterone-to-renin ratio, glomerular hyperfiltration resolves, and urinary potassium and hydrogen ion excretion are reduced (Table 1). Given the resolution of glomerular hyperfiltration, curative adrenalectomy results in a decrease in the estimated glomerular filtration rate (eGFR); this rise in creatinine and decline in eGFR is usually not reflective of acute kidney injury, rather represents an 'unmasking' of prior underlying chronic kidney disease that was not recognized pre-operatively due to the reliance on creatinine to calculate the eGFR (35, 36, 37, 38, 39). Elderly patients (65 years and older) are particularly prone to more significant eGFR decline and corresponding hyperkalemia following curative adrenalectomy (53).

The method used for determining lateralization of primary aldosteronism (adrenal CT/MRI alone vs adrenal venous sampling) influences biochemical cure rates following unilateral adrenalectomy. Williams *et al*. showed that complete biochemical success rates were significantly lower in patients who underwent adrenal CT alone (80%) compared with those who underwent adrenal venous sampling (93%) (59). This observation highlights the fact that the use of adrenal imaging alone, without adrenal venous sampling, can often lead to primary aldosteronism subtype misclassification (65, 66, 67, 68, 69, 70).

**Table 1** Expected biochemical and clinical sequelae of treatments for primary aldosteronism including: curative adrenalectomy for unilateral disease, non-curative unilateral adrenalectomy for bilateral disease, MR antagonist therapy, and dietary sodium restriction.

| Parameters | Curative adrenalectomy for unilateral disease | Non-curative unilateral adrenalectomy for bilateral disease | MR antagonist therapy | Dietary sodium restriction |
|---|---|---|---|---|
| Aldosterone | ↓↓ | ↓ | ↑ | ↑ |
| Renin | ↑↑ | ↑↑ | ↑↑ | ↑ |
| ARR | ↓↓ | ↓ | ↓ | ↓ |
| Potassium | ↑ | ↑ | ↑ | ↑ |
| Base excess/ alkalosis | ↓ | ↓ | ↓ | ↓ |
| eGFR | ↓ | ↓ | ↓ | ↓ |
| Blood pressure | ↓↓ | ↓ | ↓ | ↓ |
| Risk for incident cardiovascular and kidney disease | ↓* | Unknown | ↓* | ↓# |

*Observations from longitudinal cohort studies comparing curative adrenalectomy with MR antagonist therapy; #Observations from population-based studies evaluating dietary sodium restriction in essential hypertension.





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In summary, the most notable biochemical consequences of curative unilateral adrenalectomy for unilateral primary aldosteronism include: a substantial decrease in aldosterone, an increase in renin, a decrease in the aldosterone-to-renin ratio, normalization of serum potassium, resolution of metabolic alkalosis, and a decrease in eGFR. These expected changes are similar, but more pronounced, when compared to non-curative unilateral adrenalectomy for bilateral primary aldosteronism (discussed in more detail below), and the expected effects of medical therapy (Table 1) (17, 35, 71).

## Clinical efficacy of curative adrenalectomy for unilateral primary aldosteronism

Despite the longstanding guideline recommendation for curative adrenalectomy as the treatment of choice for unilateral primary aldosteronism (2), there are no robust or randomized controlled trials to provide high-grade evidence in support of this recommendation. The best evidence available to support curative adrenalectomy, as opposed to MR antagonist-based medical therapy, is derived from observational data. Early studies demonstrated that among the majority of primary aldosteronism patients with known aldosterone-producing adenomas who were treated medically rather than surgically, MR antagonist therapy was effective in normalizing both blood pressure and serum potassium (72, 73). However, these studies did not address long-term differences in cardiometabolic outcomes between adrenalectomy and MR antagonist therapy, much of which may occur independent of blood pressure (45).

Of the available observational studies comparing long-term cardiometabolic outcomes between adrenalectomy and MR antagonist therapy among primary aldosteronism patients, a notable limitation is that among primary aldosteronism patients currently treated with adrenalectomy, virtually all have unilateral primary aldosteronism, while the majority of primary aldosteronism patients with MR antagonist therapy have bilateral primary aldosteronism. While unilateral and bilateral primary aldosteronism share a similar pathophysiology, they do differ in several key areas including distribution of age, sex, and severity of presentation (74, 75). Further, as it is known that only a fraction of the most apparent cases of primary aldosteronism are ever diagnosed (1, 3, 4, 5, 6), observational studies evaluating treatment outcomes harbor inherent selection and referral biases, and exclude the many cases of milder, and likely bilateral, primary aldosteronism that are routinely undiagnosed. Nevertheless, in the absence of randomized controlled trials, these observational studies remain the best available evidence with which to compare adrenalectomy and MR antagonist therapy in primary aldosteronism.

Early observational data from Catena *et al.* comparing long-term cardiovascular outcomes between primary aldosteronism patients treated with adrenalectomy, primary aldosteronism patients treated with MR antagonist therapy, and a comparator group of patients with essential hypertension suggested no difference in long-term cardiovascular risk among these groups (9). However, this study was limited in power to detect differences in cardiovascular risk due to a sample size of only 54 primary aldosteronism patients (29 with unilateral primary aldosteronism and 25 with bilateral primary aldosteronism) (9). Recently, we compared long-term cardiovascular risk between 205 primary aldosteronism patients with unilateral disease treated with unilateral adrenalectomy, 602 primary aldosteronism patients with bilateral disease treated with MR antagonists, and a comparator group of >40 000 patients with essential hypertension (17). We observed that despite similar blood pressure control between the groups, primary aldosteronism patients treated with MR antagonists had a substantially higher risk for incident cardiovascular events compared to primary aldosteronism patients treated with curative adrenalectomy (hazard ratio (HR) 3.27 (95% CI 1.93, 5.55)) or comparable patients with essential hypertension (HR=1.91 (95% CI 1.63, 2.25)). In contrast, primary aldosteronism patients treated with curative adrenalectomy had a lower risk for incident cardiovascular events when compared to patients with essential hypertension (HR 0.58 (95% CI 0.35–0.97)) (17). However, when MR antagonist therapy resulted in a substantial increase in renin activity, the risk for incident cardiovascular events was observed to be no different than comparable patients with essential hypertension and similar to those who underwent curative adrenalectomy. These findings suggest the superior efficacy of surgical adrenalectomy, but also suggest that when MR antagonist therapy can be titrated to achieve a similar physiology to adrenalectomy, adverse outcome rates may be reduced to approximate, but not quite capitulate, the effects of adrenalectomy (Table 1).

Additionally, curative adrenalectomy in primary aldosteronism has been shown to have a beneficial effect in terms of preventing incident atrial fibrillation compared with MR antagonist therapy. Rossi *et al.* found that primary aldosteronism patients treated with MR





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antagonist therapy remained at higher risk for incident atrial fibrillation compared with essential hypertension patients (HR 1.82 (95% CI 1.08–3.08)) while primary aldosteronism patients treated with adrenalectomy had no significant difference in risk compared with essential hypertension patients (23). A separate study showed that this increased risk for incident atrial fibrillation among primary aldosteronism patients treated with MR antagonists versus adrenalectomy was driven primarily by those patients whose renin remained suppressed, whereas a rise in renin was associated with a similar incident event rate as adrenalectomy (24).

In addition to improved cardiovascular outcomes, curative adrenalectomy in primary aldosteronism is associated with other long-term health benefits. In a large population-based study of 2367 primary aldosteronism patients and 9468 propensity score-matched essential hypertension patients, Wu *et al.* showed that primary aldosteronism patients treated with unilateral adrenalectomy had a decreased risk for incident diabetes mellitus compared with essential hypertension patients (HR 0.60, $P < 0.01$). In contrast, primary aldosteronism patients treated with MR antagonists had an increased risk for incident diabetes mellitus compared with essential hypertension patients (HR 1.16, $P < 0.001$) (28); a finding also suggested by other large observational studies (17).

To examine the effects of curative adrenalectomy on long-term kidney function in primary aldosteronism, a recent study compared 120 primary aldosteronism patients treated with curative adrenalectomy, 400 primary aldosteronism patients with bilateral treated with MR antagonists, and >15,000 matched patients with essential hypertension (35). This study found that primary aldosteronism patients treated with MR antagonists had a steeper decline in eGFR (−1.6 vs −0.9 mL/min/1.73 $m^2$ per year, $P < 0.001$) and a correspondingly higher rate of incident chronic kidney disease (HR: 1.63 (95% CI 1.33–1.99)) compared with essential hypertension patients. In contrast, primary aldosteronism patients treated with curative adrenalectomy had no significant difference in eGFR decline (−0.8 vs −0.9 mL/min/1.73 $m^2$ per year, $P = 0.53$) or incident chronic kidney disease (HR: 0.71 (95% CI 0.39–1.30)) (35). Similarly, another large population-based study showed that primary aldosteronism patients treated with adrenalectomy had a reduced risk of end-stage kidney disease compared to essential hypertension (HR: 0.38 (95% CI 0.19–0.76)) while there was no difference between primary aldosteronism treated with MR antagonists and essential hypertension (HR: 1.08 (95% CI 0.83–1.39)) (41).

Targeted therapies for primary aldosteronism, adrenalectomy and MR antagonists, have both been shown to improve quality of life (61, 76, 77). However, the quality of life metrics for patients following curative adrenalectomy improved to a greater degree, and to the level of the general population, while the quality of life metrics for patients treated with MR antagonists did not improve to the same degree (77).

Finally, a number of large population-based studies have demonstrated a reduction in mortality in primary aldosteronism following curative adrenalectomy compared with essential hypertension that is not seen with MR antagonist therapy (18, 28). One study observed that the mortality rate for primary aldosteronism treated with MR antagonist therapy was up to 34% higher (HR 1.34 (95% CI 1.06–1.71)) compared with essential hypertension (17).

## Biochemical and clinical sequelae of non-curative unilateral adrenalectomy for bilateral primary aldosteronism

When adrenal venous sampling demonstrates bilateral primary aldosteronism, the general treatment dogma is to prescribe lifelong MR antagonist therapy (2, 78). Although the premise for this recommendation is well-intended and based on physiologic principles, it assumes superiority over the potential benefit of non-curative unilateral adrenalectomy to attenuate the severity of disease in certain patients with bilateral primary aldosteronism. It should be noted that there is no high-grade clinical trial evidence supporting lifelong MR antagonist therapy in bilateral PA (as opposed to conventional non-MR antagonist medications, amiloride, or unilateral non-curative adrenalectomy); rather, it has been accepted as convention for decades based on logical assumptions.

Important questions regarding the ethics, practicality, and cost-effectiveness of any treatment approach must be evaluated in every instance. MR antagonist therapy may be suited for most, or many, patients with bilateral primary aldosteronism; however, given the efficacy of surgical adrenalectomy, it is worth considering this option in certain circumstances. For example, for a patient with bilateral primary aldosteronism:

- Is lifelong MR antagonist therapy the ideal choice for a patient who has a substantial burden of established cardiovascular disease or advanced chronic kidney disease? Could the risk for incident cardiovascular events and/or end stage kidney disease be more





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effectively lowered with non-curative unilateral adrenalectomy to attenuate the burden of aldosterone excess prior to instituting MR antagonist therapy?

- Is lifelong MR antagonist therapy the ideal choice for a patient who has bilateral primary aldosteronism characterized by gross asymmetry in aldosterone lateralization indicating that one adrenal produces the majority of aldosterone? Could surgical resection of the dominant side provide greater clinical and biochemical results when compared to lifelong MR antagonist therapy without any antecedent surgical intervention?
- Is lifelong MR antagonist therapy the ideal recommendation for a patient who already takes many medications (e.g. 3–4 anti-hypertensive medications and 4–6, or more, other medications)? Is the risk of compounding polypharmacy over a lifetime an indication to consider a non-curative surgical procedure?
- Is lifelong MR antagonist therapy the ideal choice for a young patient with bilateral primary aldosteronism? For example, is it reasonable to consider that a 43-year-old patient could take MR antagonists successfully for the rest of their life? Alternatively, could the risk for incident cardiovascular and kidney disease be better attenuated with a surgical approach preceding the institution of MR antagonists?

To be clear, the answers to these difficult questions are not established; there are no high-grade comparative trials or longitudinal studies that provide sufficient data to develop evidence-based recommendations. Further, the use of MR antagonists, as opposed to surgical intervention, may be the obligate default given its relative cost-effectiveness and low resource utilization; however, the long-term efficacy on health quality and economics has not been robustly analyzed. Beyond personal anecdotes and clinical experiences, there have been some case series that provide useful insights into the biochemical and clinical efficacy of non-curative unilateral adrenalectomy. Biglieri *et al.* observed 50 years ago that non-curative unilateral adrenalectomy for idiopathic aldosteronism lowered blood pressure and aldosterone production; however, over time, the severity of aldosteronism slowly recurred (62). Groth *et al.* evaluated the efficacy of non-curative unilateral adrenalectomy for bilateral primary aldosteronism ($n$ = 12) in comparison to curative adrenalectomy for unilateral primary aldosteronism ($n$ = 38) in 1985 (79). Five years following the intervention, patients who had non-curative adrenalectomy had a substantial reduction in blood pressure, a modest decrease in aldosterone levels, a substantial increase in renin that paralleled the rise in renin seen in those who underwent curative unilateral adrenalectomy (from ~0.30 ng/mL/h to more than 2.0 ng/mL/h), and near normalization of serum potassium (79). Thus, although unilateral adrenalectomy did not cure patients with bilateral primary aldosteronism, it did provide a durable improvement in blood pressure, in the number of blood pressure medications needed, in the severity of hypokalemia, and a large increase in renin.

A similar, but larger and longer, series was reported by Sukor *et al.* in 2009 who studied the clinical and biochemical sequelae of non-curative unilateral adrenalectomy in 51 patients with bilateral primary aldosteronism treated over a 22-year span (80). Non-curative unilateral adrenalectomy was performed to attenuate the severity of excess aldosterone for patients who could not tolerate MR antagonists and/or had ineffective blood pressure control with MR antagonist therapy. The adrenal gland chosen for removal either had a higher aldosterone-to-cortisol ratio on adrenal venous sampling than the contralateral gland, and/or was larger or more morphological abnormal on imaging. Within 1 year of the surgery, 15% of patients experienced a cure of their hypertension and 40% more patients had their blood pressure under control. In addition, unilateral non-curative adrenalectomy resulted in a 18% decline in aldosterone levels, a 500% increase in renin (~3.3 to ~16.6 mU/L), a substantial decline in the aldosterone-to-renin ratio, normalization of serum potassium, an increase in serum creatinine (and hence, lower eGFR), and a reduction in left ventricular mass index (80).

While distinguishing between unilateral and bilateral forms of primary aldosteronism have been a traditional nomenclature and clinical decision-making node, a recent study by Desrochers *et al.* suggests that many, or most, instances of lateralizing (and presumptively unilateral) primary aldosteronism may actually exhibit mild aldosterone excess from the contralateral gland (81). This demonstration, that contralateral aldosterone suppression during adrenal venous sampling is a rare finding in lateralizing cases, provides support for the hypothesis that truly unilateral disease in primary aldosteronism may be rare, and may potentially support the hypothesis that aldosterone-producing cell clusters are a prevalent cause of bilateral primary aldosteronism pathogenesis (81). Recent techniques employing segmental selective adrenal venous sampling to precisely map the location of aldosterone production within the adrenal gland have shown promise for the use of partial adrenalectomy, rather than complete adrenalectomy (82). This procedure has been shown to induce a high rate of partial, or complete,





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biochemical and clinical success for both unilateral and bilateral disease; however, it is not broadly available and has not been widely replicated yet.

In summary, although lifelong MR antagonist therapy is recommended as the default option because it is a cost-effective and well-tolerated treatment for patients with bilateral primary aldosteronism, there does exist fairly consistent evidence from case series supporting the utility of non-curative unilateral adrenalectomy (complete or partial) to improve the clinical and biochemical features of the disease. Importantly, unilateral adrenalectomy in bilateral primary aldosteronism can induce all of the physiologic changes that are associated with successful outcomes in curative unilateral adrenalectomy and with MR antagonist therapy (Table 1); therefore, this option should be considered and discussed with patients in a manner that prioritizes their values, the risks and benefits of either option, associated financial costs, and long-term quality of life.

## A practical algorithm for surgical indications in primary aldosteronism

We propose this algorithm as a practical approach to considering surgical therapy for primary aldosteronism. These recommendations are based on published evidence and our personal clinical experiences in treating patients with primary aldosteronism, and place emphasis on the fact that reducing long-term exposure to excess aldosterone is associated with improved outcomes and mortality (Fig. 1).

When primary aldosteronism is confirmed to be unilateral (ideally with adrenal venous sampling), we strongly recommend a curative unilateral adrenalectomy performed via a laparoscopic approach. This procedure is relatively safe, is of minimal risk, and imparts a high likelihood for durable improvements in blood pressure, reductions in medication use, normalization of potassium, alkalosis, and renin, and is associated with a lower risk for incident cardiovascular, metabolic, and kidney disease. When patients are unwilling or unable to undergo curative unilateral adrenalectomy, MR antagonist therapy should be used as the alternative.

When bilateral disease is confirmed on adrenal venous sampling, we recommend first evaluating the risks and benefits of instituting lifelong MR antagonist therapy versus a unilateral non-curative adrenalectomy to attenuate the severity of disease. This decision must be made on a case-by-case basis and after a detailed discussion with the patient regarding the potential benefits, risks, and unknown implications. We recognize that in many or most instances, clinicians and patients may not feel confident in deciding on a non-curative adrenalectomy without first undertaking a trial of MR antagonist therapy; this too, is a perfectly reasonable approach, discussed below. Regardless, we encourage this discussion up-front and with transparency. Factors to consider when making this decision include the age of the patient, established cardiovascular and/or kidney disease, established polypharmacy, and the presence of grossly asymmetric disease (as quantified by asymmetric aldosterone-to-cortisol ratios on adrenal venous sampling and/or gland morphologies on cross-sectional imaging) (Fig. 1). If laparoscopic, non-curative, unilateral adrenalectomy is performed, it is anticipated that there will likely be clinical and biochemical improvement; however, primary aldosteronism will not be cured, and therefore, post-operative MR antagonist therapy is still indicated, albeit at lower and more manageable doses.

When MR antagonist therapy is recommended, we strongly advise counseling on dietary sodium reduction since lowering sodium intake effectively lowers the fuel that modulates disease severity, and is an intervention that when instituted correctly is known to lower blood pressure and increase renin akin to other medical and surgical interventions (Table 1) (78, 83). Optimization of MR antagonist therapy requires gradual titration of the dose toward milestones of success (78); normalization of blood pressure, normalization of serum potassium (ideally in the mid- to high-normal range), and ideally normalization (or an unsuppression) of renin (17, 78, 84). The achievement of these clinical and biochemical benchmarks essentially parallels the outcomes that are expected to be achieved by surgical interventions. MR antagonist therapy can be considered to be sub-optimal when these clinical and biochemical milestones are not achieved, and/or when there are obstacles that prevent the realization of these milestones, such as recurrent hyperkalemia due to chronic kidney disease, and/or high doses of beta-adrenergic antagonists that lower renin (71), and/or the use of renin activity assays that do not reliably report very low values, and/or intolerance or adverse effects due to MR antagonists (Fig. 1). These obstacles are common and can become more challenging over time, with older age, and when there is concomitant chronic kidney disease. Amiloride (85), other anti-hypertensive agents, and patiromer (86) can all be used as adjunct therapies in this scenario; however, they may further compound the risk of polypharmacy and potential drug interactions and adverse effects. We suggest that the inability to optimize medical





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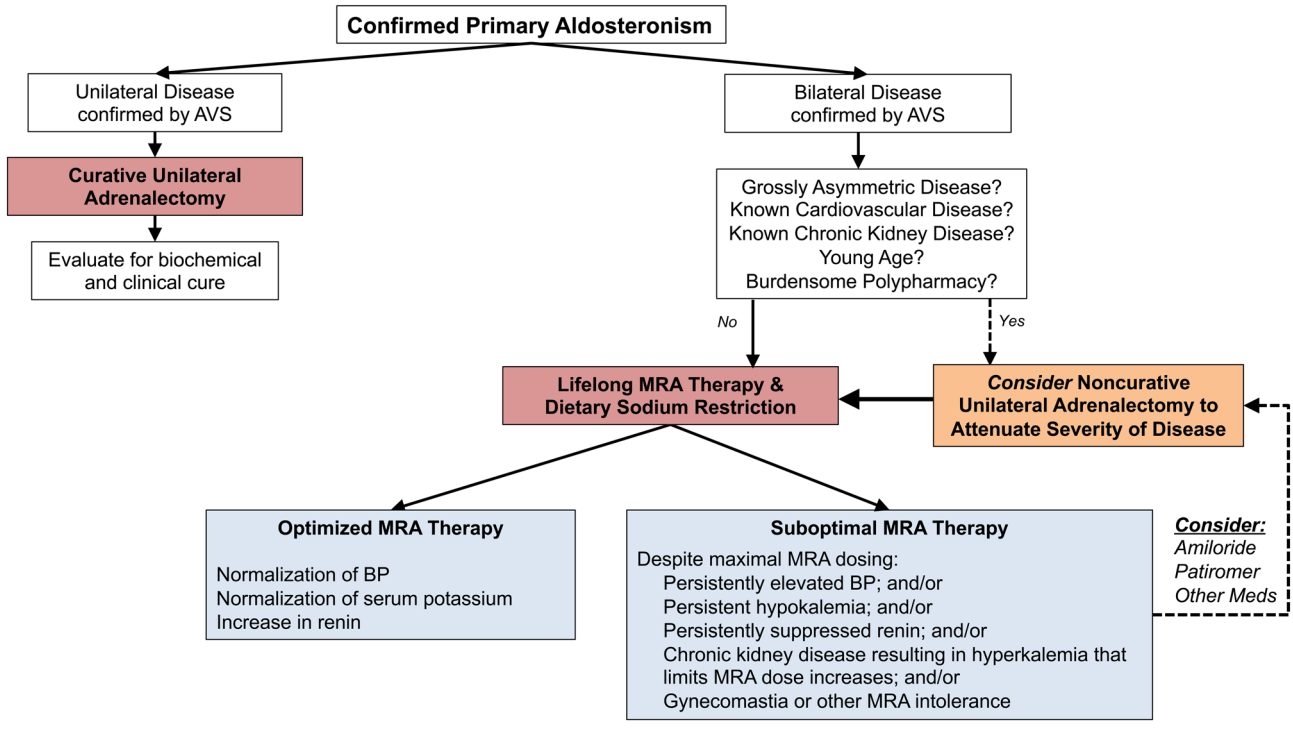


**Figure 1**

Practical algorithm for primary aldosteronism treatment. When primary aldosteronism is determined to be unilateral in nature, a curative unilateral adrenalectomy should be strongly recommended as this is the most effective approach to induce durable improvements in blood pressure, serum potassium, and long-term cardiometabolic risk. When primary aldosteronism is determined to be bilateral in origin, the conventional treatment option is to initiate mineralocorticoid receptor antagonists; dietary sodium restriction should also be simultaneously enforced since the combination of these two medical interventions is most likely to induce biochemical and clinical improvements. A currently unconventional, but likely effective approach, is to consider a non-curative unilateral adrenalectomy. This approach can be considered for patients with grossly asymmetric disease, a high burden of known cardiovascular and/or kidney disease, those that are very young and may have to endure decades of medical therapy and polypharmacy, or when medical therapy cannot be optimized.

therapy should prompt another opportunity to consider non-curative unilateral adrenalectomy to attenuate the severity of disease, achieve better blood pressure control, reduce the burden of medications, and potentially lower the risk of future cardiovascular and kidney disease. Since longer durations of excess aldosterone exposure can induce irreversible heart failure and vasculopathies (hypertension and disease of the coronary, cerebral, and renal vasculature), it is important to consider these decisions as early, and frequently, as possible.

## Bilateral adrenalectomy for bilateral primary aldosteronism

Bilateral adrenalectomy for bilateral primary aldosteronism is not recommended or supported by systematic evidence; however, there are anecdotal experiences described in selected cases (62). Although the procedure is curative for primary aldosteronism, in general, inducing iatrogenic primary adrenal insufficiency is not desirable, and in some instances, potentially unethical. It should be noted, however, that most patients with bilateral surgical adrenalectomy (for indications other than primary aldosteronism) will experience a high quality of life when cared for by an endocrinologist with experience in prescribing supplemental adrenal steroids and educating patients regarding management of illness and other health stressors. Thus, in situations where medical therapy for bilateral primary aldosteronism remains sub-optimal, and unilateral non-curative adrenalectomy is unable to dramatically improve the clinical and biochemical risk factors that portend a high risk for incident cardiovascular and kidney disease, an individualized decision to perform





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another adrenalectomy can be made. The driving force underlying this decision should be a convincing argument that the long-term risks of sub-optimally treated primary aldosteronism outweigh the risks of having long-term primary adrenal insufficiency. We strongly suggest that these decisions be made by endocrinologists with substantial experience with primary adrenal insufficiency and primary aldosteronism, on a case-by-case basis, and after detailed and informed conversations with the patient regarding the tradeoffs of this unconventional decision.

## Conclusions

Primary aldosteronism is a common, though vastly under-recognized, disorder associated with high rates of cardiometabolic and kidney disease. Surgical adrenalectomy has long been considered the mainstay of treatment for patients with unilateral primary aldosteronism since this operation can cure the disease, can be performed laparoscopically, can correct the biochemical abnormalities inherent to the disease, improve blood pressure control, and improve long-term cardiometabolic risk. In contrast, lifelong MR antagonist therapy has long been considered the mainstay of treatment for patients with bilateral primary aldosteronism. However, data on the benefits of MR antagonists in reducing long-term cardiometabolic risk are less robust (and/or more challenging to achieve) than with adrenalectomy, and intolerance and side effects commonly prevent their lifelong use. Unilateral adrenalectomy in bilateral primary aldosteronism (where the goal is disease attenuation rather than disease cure) has been shown to improve the clinical and biochemical features of the disease and can be considered on a case-by-case basis in situations where long-term MR antagonist use is not feasible and/or cannot be optimized (e.g. chronic kidney disease, gynecomastia or other intolerance, uncontrolled blood pressure/hypokalemia despite maximal dosing, polypharmacy) or where the long-term pathologic consequences of autonomous aldosterone excess are likely to be particularly burdensome (e.g. young patient, existing cardiovascular or kidney disease).

**Declaration of interest**

A V reports consulting, unrelated to the contents of this work, from Corcept Therapeutics, HRA Pharma, Mineralys. The other authors have nothing to disclose.

**Funding**

The authors acknowledge funding from the National Institutes of Health grants R01DK115392 (A V), R01DK16618 (A V) and R01HL153004 (A V).

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Received 28 July 2020
Revised version received 24 September 2020
Accepted 30 September 2020



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