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Primary Aldosteronism: Cardiovascular Outcomes Pre- and Post-treatment

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Abstract

Purpose of Review Primary aldosteronism (PA) is a common form of hypertension characterized by autonomous aldosterone secretion from one or both adrenal glands. The purpose of this review is to synthesize recent research findings regarding cardiovascular disease risk in PA both pre- and post-targeted therapy.

Recent Findings Previously considered a rare disease, recent prevalence studies demonstrate that PA is actually a very common, yet vastly under-diagnosed, etiology of hypertension. Prior to targeted therapy, PA is associated with substantially higher rates of cardiovascular disease compared with essential hypertension. Surgical adrenalectomy is highly effective in curing or improving hypertension as well as mitigating cardiovascular disease risk in patients with unilateral PA. For the remainder of PA patients, MR antagonists are recommended; however, several recent studies have brought into question their effectiveness in improving cardiovascular outcomes.

Summary PA is a common cause of hypertension that leads to disproportionately high rates of cardiovascular disease. Future studies are needed to enhance the clinical approach to both identification and treatment of patients with PA to optimize long-term cardiovascular outcomes.

Keywords Primary aldosteronism · Primary hyperaldosteronism · Conn's syndrome · Mineralocorticoid receptor antagonist · Cardiovascular disease · Atrial fibrillation

Introduction

Primary aldosteronism (PA) is the most common form of secondary hypertension and is attributable to autonomous, renin-independent hyper-secretion of aldosterone from one or both adrenal glands. Previously considered a rare disease, recent prevalence studies demonstrate that PA is actually a very common, yet vastly under-diagnosed, etiology of hypertension. Compared with essential hypertension, PA results in substantially higher rates of cardiovascular disease, independent of blood pressure. The guideline-recommended targeted therapies for PA include surgical adrenalectomy and lifelong mineralocorticoid receptor (MR) antagonist therapy. In this review, we will focus on the cardiovascular consequences of PA both pre- and post-targeted therapy.

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Primary Aldosteronism: the Basics

Pathophysiology

In normal physiology, aldosterone secretion is mediated by three primary regulators: renin/angiotensin II, potassium, and adrenocorticotropic hormone (ACTH). In contrast, the hallmark of PA is autonomous aldosterone hyper-secretion from one or both adrenal glands, independent of these regulatory pathways.

In the kidney, aldosterone acts primarily in the distal tubules and collecting ducts of the nephron where it binds to the MR of the principal cell, resulting in potent sodium reabsorption via epithelial sodium (ENaC) channels and a corresponding excretion of potassium and hydrogen ions in order to maintain electroneutrality. Water reabsorption consequent to the ENaC-mediated sodium reabsorption induces chronic volume expansion resulting in suppression of both renin and angiotensin II. Suppression of angiotensin II results in enhanced sodium delivery to the distal tubules and collecting ducts of the nephron, thereby resulting in further enhanced ENaC-mediated sodium reabsorption and PA's classic clinical triad of hypertension, hypokalemia, and metabolic alkalosis.

Notably, aldosterone also binds to the extra-renal MR in other tissues such as the heart and vasculature. Along with the chronic volume expansion resultant to activation of the renal MR, activation of the extra-renal MR further contributes to vascular disease progression via a variety of mechanisms including fibrosis of both the myocardium and vascular endothelium, endothelial dysfunction, and increased arterial stiffness. These deleterious effects may help explain the disproportionately high rates of cardiovascular disease seen with PA [1–11].

Prevalence

While the long-standing perception in the medical field was that PA is a rare cause of hypertension, multiple recent prevalence studies in a variety of countries have disproven this myth. In fact, it is increasingly recognized that PA is a very common, though vastly under-diagnosed, etiology of hypertension, accounting for 5–10% of all cases of hypertension [12, 13, 14, 15••, 16, 17, 18, 19, 20] and 12–20% of cases of resistant hypertension [15••, 16, 21–23].

A recent Italian study by Monticone et al. highlighted just how common PA is in the hypertensive population [15••]. In this study, 1672 primary care patients with hypertension were tested for PA using guideline-recommended diagnostic thresholds [24••]. The results of this study revealed that 6% of all cases of hypertension were attributable to PA. Additionally, among patients with more severe hypertension (defined as an untreated blood pressure of > 160/100 mmHg), the prevalence of PA increased to 12%.

An important sub-classification of PA is whether aldosterone is autonomously secreted from one adrenal gland (unilateral; most commonly due to an aldosterone-producing adenoma [APA]) or both adrenal glands (bilateral; most commonly due to bilateral adrenal hyperplasia [BAH]) as this distinction helps to determine the recommended treatment approach. Multiple studies have shown that approximately one-third of PA cases are due to unilateral disease while the remaining two-thirds of PA cases are due to bilateral disease [15••, 16, 20].

Diagnostic Testing

Making a diagnosis of PA generally involves three stages: screening, confirmation, and lateralization.

Screening

Table 1 lists the current guideline recommendations for whom to screen for PA.

Despite these guideline recommendations, the vast majority of patients who meet these criteria never undergo screening for PA [25]. Additionally, given the mounting evidence of the prevalence of PA among more mild forms of hypertension (patients who would not meet the screening criteria listed above) [15••, 16, 26, 27], there is a growing push to expand the criteria for whom should be screened [15••, 28, 29].

The most widely accepted screening test for PA is the aldosterone-to-renin ratio (ARR) [24••]. While the accepted cutoffs for a positive ARR screen vary center-to-center, the most widely accepted cutoff for a positive screen is an ARR > 30 ng/dL per ng/mL/h [24••, 30]. In addition to meeting this ARR cutoff, the absolute values of both renin and aldosterone should also be taken into consideration for what constitutes a positive screen. At the time of diagnosis and prior to targeted therapy, the renin level in PA is universally suppressed (e.g., plasma renin activity [PRA] < 1.0 ng/mL/h). In regard to a minimum cutoff for the plasma aldosterone concentration (PAC), there is much more debate. Many clinicians use a PAC cutoff of > 15 ng/dL [24, 30] though there are clearly PA cases, particularly BAH, that exist below this threshold [16, 31]; therefore, other clinicians use more conservative PAC cutoffs (e.g., > 10 or > 6 ng/dL) depending on the desired sensitivity and specificity of testing. In most scenarios, a patient's antihypertensive medications can be continued during ARR testing—a topic which has been addressed in several recent PA review articles [29, 32].

Confirmation

Confirmatory testing is often required to make the diagnosis of PA. The exception to this is when the initial

Table 1 Current recommendations for whom to screen for primary aldosteronism as per Endocrine Society Guidelines [24••]

Current recommended indications for primary aldosteronism screening
Blood pressure > 150/100 mmHg on 3 consecutive measurements on separate days
Blood pressure > 140/90 mmHg resistant to 3 antihypertensive medications (including a diuretic)
Blood pressure < 140/90 mmHg controlled with ≥ 4 antihypertensive medications
Hypertension + spontaneous or diuretic-induced hypokalemia
Hypertension + adrenal incidentaloma
Hypertension + sleep apnea
Hypertension + family history of early onset hypertension or stroke prior to age 40
Hypertension + 1st degree relative with primary aldosteronism

presentation is overwhelmingly convincing for the diagnosis of PA: positive ARR screen, spontaneous hypokalemia, undetectable renin, and PAC > 20 ng/dL. In this scenario, confirmatory testing is unnecessary and the diagnosis of PA can be assumed [24••]. In all other scenarios, confirmatory testing is recommended following a positive screen for PA. The type of confirmatory testing used varies by center but all are designed to determine whether aldosterone secretion is suppressible. The four recommended confirmatory tests are oral sodium load, saline infusion, fludrocortisone suppression, and captopril challenge testing. The recommended protocols and interpretations for each of these tests are described in detail in the Endocrine Society Guidelines [24••].

Lateralization

After the diagnosis of PA has been established, the next step is to determine whether the source of autonomous aldosterone secretion is from one adrenal gland (unilateral) or both adrenal glands (bilateral). This distinction is critical as it will guide treatment recommendations. Lateralization general involves two steps: (1) cross-sectional imaging via adrenal-protocol computed tomography (CT) or magnetic resonance imaging (MRI), and (2) adrenal vein sampling (AVS). CT or MRI is recommended for all PA patients, even if they would not pursue surgical treatment, in order to exclude adrenocortical carcinoma. However, if a patient would pursue surgical treatment, cross-sectional imaging alone is generally considered insufficient to determine disease lateralization as imaging alone can result in misclassification (unilateral versus bilateral) in a substantial proportion of cases [33, 34, 35, 36••, 37]. One notable exception to this is in patients < 35 years of age with spontaneous hypokalemia, marked aldosterone excess, and a clear unilateral adenoma on cross-sectional imaging. In this scenario, the adenoma can be assumed to be the source of autonomous aldosterone secretion and AVS can be bypassed [34, 38, 39]. AVS protocols and interpretation vary by center and are addressed in detail in several recent review articles [40, 41].

Treatment Guidelines

For patients with unilateral PA who are healthy enough and willing to undergo surgery, the guidelines recommend curative adrenalectomy. For all patients with bilateral PA and those with unilateral PA who are either unwilling or unable to undergo surgery, guidelines recommend lifelong MR antagonist medical therapy (most commonly spironolactone or eplerenone) along with dietary sodium restriction [24••].

Cardiovascular Outcomes: Pre-targeted Therapy

Numerous observational studies have consistently shown that prior to targeted therapy (i.e., surgical adrenalectomy or MR antagonist therapy), patients with PA experience disproportionately higher rates of adverse cardiovascular events compared with patients with essential hypertension, independent of blood pressure control.

Congestive Heart Failure/Left Ventricular Hypertrophy

Long-term autonomous aldosterone hyper-secretion and the consequent MR over-activation present in PA result in significant changes to both cardiac structure and function. While the hypertensive effects of PA are responsible for some of these findings, many of these changes in cardiac structure and function in PA develop independent of blood pressure. Specifically, PA patients develop proportionately higher rates of myocardial fibrosis compared with other forms of hypertension, independent of blood pressure [2, 9, 10, 42, 43].

Echocardiographic studies comparing PA patients to age- and blood pressure-matched patients with essential hypertension show that PA patients have increased left ventricular mass and a higher rate of overt left ventricular hypertrophy [42–49]. Correspondingly, PA patients demonstrate substantially increased rates of diastolic dysfunction compared with patients with essential hypertension [43–46, 48]. Several recent echocardiographic studies assessing global longitudinal strain further suggest that PA patients may also develop a subclinical decline in left ventricular systolic function [44, 50].

These abnormalities in cardiac structure and function in PA result in high rates of symptomatic congestive heart failure. Multiple observational studies comparing PA and essential hypertension have consistently demonstrated substantially higher rates of congestive heart failure, independent of blood pressure [17, 47, 51, 52••, 53, 54••, 55, 56]. A recent meta-analysis by Monticone et al. attempted to synthesize many of these observational studies and reported that PA patients have more than two-fold higher odds for developing congestive heart failure compared with patients with essential hypertension, independent of blood pressure (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.11 to 3.78) [54••].

Atrial Fibrillation

Currently, there is a growing interest in the role aldosterone, and its interaction with the MR, as an important mediator in the development and persistence of atrial fibrillation. Several recent human and animal studies have demonstrated that aldosterone promotes atrial fibrillation via atrial fibrosis, cardiac remodeling, and conduction disturbances even beyond the PA

population [57, 58, 59, 60•, 61]. For instance, Takemoto et al. demonstrated that eplerenone reduced the ability to induce atrial fibrillation and delayed the development of persistent atrial fibrillation in a sheep model of atrial fibrillation [60•]. Similarly, in a sub-analysis of the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) study, patients with congestive heart failure who were randomized to eplerenone rather than placebo experienced a 42% lower risk for developing new onset atrial fibrillation (hazard ratio [HR] 0.58, 95% CI 0.35 to 0.96) [59].

PA, an extreme case of aldosterone exposure, has offered an ideal patient population with which to investigate the role of aldosterone in the development of atrial fibrillation. Indeed, numerous studies describe a substantially higher rate of incident atrial fibrillation among patients with PA compared with blood pressure-matched patients with essential hypertension [15, 47, 51, 52••, 53, 55, 62, 63, 64••, 65••]. Monticone et al. reported that PA patients have greater than 3.5-fold higher odds for developing atrial fibrillation compared with patients with essential hypertension, independent of blood pressure (OR 3.52, 95% CI 2.06 to 5.99) [54••].

Stroke

As stroke is the most common severe complication of atrial fibrillation [66, 67], it is not surprising that PA patients also have substantially higher rates of stroke compared with patients with essential hypertension [15, 51, 52••, 53, 55, 56, 62, 68]. Beyond the increased stroke risk related to higher rates of atrial fibrillation, PA patients may also be at higher risk for incident stroke due to the deleterious effects that aldosterone and MR over-activation have on the vessel wall including oxidative stress, inflammation, fibrosis, and remodeling [3, 4, 6, 69]. Monticone et al. report that PA patients have greater than 2.5-fold higher odds of stroke compared with patients with essential hypertension, independent of blood pressure (OR 2.58, 95% CI 1.93 to 3.45) [54••].

Myocardial Infarction

Prior to targeted therapy, PA patients also suffer substantially higher rates of myocardial infarction compared with blood pressure-matched patients with essential hypertension [15, 47, 51, 52••, 53, 55, 56, 62, 70]. Monticone et al. found that PA patients have 77% higher odds for incident myocardial infarction or coronary revascularization compared with patients with essential hypertension, independent of blood pressure (OR 1.77, 95% CI 1.10 to 2.83) [54••]. Similarly, PA patients have been shown to have higher rates of cardiovascular mortality compared with patients with essential hypertension [70].

Diabetes Mellitus and Metabolic Syndrome

Diabetes mellitus and metabolic syndrome are well-established risk factors for incident cardiovascular disease [71–74]. A growing body of evidence shows that PA is strongly associated with higher rates of diabetes mellitus and metabolic syndrome compared with essential hypertension [52••, 75–78]. This relationship between autonomous aldosterone secretion and diabetes mellitus/metabolic syndrome may further explain some of the trends described above in regard cardiovascular disease risk in PA. Much of this enhanced susceptibility to diabetes mellitus and metabolic syndrome appears to be driven by cortisol co-secretion in PA [79, 80•, 81]. A recent study compared the steroid metabolome of PA patients with that of healthy controls, patients with an inactive adrenal adenoma, patients with subclinical Cushing syndrome, and patients with overt Cushing syndrome [80•]. This study found that patients with PA had higher rates of cortisol secretion compared with all other groups except for those with overt Cushing syndrome.

Table 2 summarizes the odds ratios for these cardiovascular and metabolic outcomes from the recent meta-analysis by Monticone et al. [54••].

Cardiovascular Outcomes: Post-targeted Therapy

As opposed to the multitude of studies highlighting the disproportionately high rates of cardiovascular disease inherent to PA prior to targeted therapy with surgical adrenalectomy or MR antagonists, there has been a relative scarcity of data on whether these therapies effectively prevent adverse cardiovascular events. Many clinicians have operated on the assumption that both surgical adrenalectomy and MR antagonists are equally effective in improving cardiovascular outcomes. Recently, however, several large studies have attempted to shed light on whether surgical adrenalectomy and MR antagonist therapy each effectively mitigate cardiovascular disease risk and have brought into question the optimal treatment approach to PA [52••, 64••, 65••, 82].

Surgical Adrenalectomy

For patients with unilateral PA who are healthy enough and willing to undergo the procedure, surgical adrenalectomy is the guideline-recommended treatment [24••]. Most centers perform this procedure laparoscopically resulting in reductions in both surgical complications as well as length-of-stay [83–85]. For the majority of patients with unilateral PA, surgical adrenalectomy results in cure of (i.e., normotension off all antihypertensive medications) or reduced severity of hypertension (i.e., improved blood pressure control and/or a

Table 2 Odds of cardiovascular and metabolic outcomes in patients with primary aldosteronism prior to targeted therapy compared with patients with essential hypertension from a recent meta-analysis by Monticone et al. (Lancet Diabetes and Endocrinology, 2018) [54••]

Outcome (primary aldosteronism vs. essential hypertension)	Odds ratio (95% confidence interval)
Cardiovascular	
Congestive heart failure	2.05 (1.11 to 3.78)
Left ventricular hypertrophy	2.29 (1.65 to 3.17)
Atrial fibrillation	3.52 (2.06 to 5.99)
Stroke	2.58 (1.93 to 3.45)
Myocardial infarction/coronary revascularization	1.77 (1.10 to 2.83)
Metabolic	
Diabetes mellitus	1.33 (1.01 to 1.74)
Metabolic syndrome	1.53 (1.22 to 1.91)

reduction in the number of antihypertensive medications required) [36••, 86–93]. Additionally, most unilateral PA patients who undergo adrenalectomy experience resolution of hypokalemia, normalization of the ARR ("biochemical cure"), and improved quality of life [36••, 89, 91, 94].

In regard to long-term outcomes, surgical adrenalectomy does appear to effectively mitigate adverse cardiovascular events. The largest study to demonstrate this was a retrospective study comparing 205 patients with unilateral PA and > 40,000 patients with essential hypertension and similar blood pressure control [52••]. PA patients who underwent surgical adrenalectomy were found to have a lower 10-year risk for incident cardiovascular events (defined as a composite of myocardial infarction, heart failure, or stroke) compared with patients with essential hypertension (HR 0.58, 95% CI 0.35 to 0.97). Several additional recent studies have shown that surgical adrenalectomy in PA effectively lowers the risk of incident atrial fibrillation to a level similar to that of essential hypertension [64••, 65••, 82]. Finally, the risk for both diabetes mellitus and mortality may also be reduced in unilateral PA following adrenalectomy [78, 95].

Mineralocorticoid Receptor Antagonists

While patients with unilateral PA who undergo surgical adrenalectomy appear to have favorable outcomes as described above, the evidence is less encouraging in regard to the efficacy of MR antagonist therapy for the remainder of patients with PA. For all patients with bilateral PA, and also those with unilateral PA who are unable or unwilling to undergo surgical adrenalectomy, lifelong MR antagonist therapy is the guideline-recommended treatment [24••]. These medications act by blocking the interaction between aldosterone and the MR thereby reducing ENaC-mediated sodium reabsorption, volume expansion, and potassium and hydrogen ion excretion. Therefore, these medications are effective in reducing blood pressure and improving both potassium and acid-base balance. The two most commonly prescribed MR antagonists are spironolactone and eplerenone. When comparing these two agents, eplerenone is only about half as potent as spironolactone and has a shorter half-life and is therefore recommended to be given twice daily (as opposed to once daily with spironolactone). However, eplerenone is a more selective MR antagonist than spironolactone and, therefore, does not have the anti-androgen and progesterone agonist effects (e.g., gynecomastia in men) that frequently limit adherence to spironolactone [24••, 96].

For many years, little data existed in regard to whether the current clinical use of MR antagonists in patients in PA is effective in preventing adverse long-term health outcomes. However, a number of recent observational studies now suggest that despite MR antagonist therapy, patients with PA continue have disproportionately worse health outcomes compared with patients with essential hypertension [52••, 64••, 65••, 78, 95, 97]. Whereas PA patients treated with surgical adrenalectomy demonstrate favorable risk profiles comparable to those of patients with essential hypertension in regard to incident cardiovascular disease, diabetes mellitus, and mortality, the same cannot be said for PA patients treated with MR antagonists. A recent large observational cohort study compared cardiovascular and metabolic outcomes between 602 PA patients treated with MR antagonists and 41,853 age-matched patients with similar longitudinal blood pressure control [52••]. Despite treatment with MR antagonists, PA patients continued to have a nearly twofold higher risk (HR 1.91 [95% CI 1.63 to 2.25]) for incident cardiovascular disease (defined as a composite of myocardial infarction, heart failure, or stroke) compared with patients with essential hypertension [52••]. PA patients treated with MR antagonists also continued to have higher risk for atrial fibrillation (HR 1.93 [95% CI 1.54 to 2.62]), diabetes mellitus (HR 1.26 [95% CI 1.01 to 1.57]), and mortality (HR 1.34 [95% CI 1.06 to 1.71]) [52••].

Notably, several of these recent studies highlight that much of the excess risk for cardiovascular disease among PA patients treated with MR antagonists was limited to those whose renin remained suppressed (PRA < 1 ng/mL/h) despite MR antagonist therapy [52••, 65••]. Among the PA patients whose

renin became unsuppressed (PRA ≥ 1 ng/mL/h) with MR antagonist therapy, the risk for incident myocardial infarction, heart failure, stroke, atrial fibrillation, and mortality was effectively reduced to levels comparable to that of patients with essential hypertension. Notably, the patients who achieved an unsuppressed renin (PRA ≥ 1 ng/mL/h) were treated with higher doses of MR antagonists than those whose renin remained suppressed (PRA < 1 ng/mL/h). As discussed throughout this review, numerous studies have consistently shown that PA patients have disproportionately high rates of cardiovascular disease independent of blood pressure [51, 53, 54••, 70]. Therefore, blood pressure alone may not be an adequate biomarker of treatment adequacy in PA. In addition to blood pressure, these recent observational studies suggest that a rise in renin, reflective of adequate MR blockade inducing reversal of the chronic state of volume expansion inherent to PA, may be a clinically useful biomarker to help guide MR antagonist dosing to optimize cardiovascular outcomes [52••, 65••]. However, future prospective studies are needed to further validate the clinical utility of renin as a biomarker of adequate MR blockade in PA.

Conclusions

PA is a common, yet vastly under-diagnosed, form of hypertension due to autonomous aldosterone secretion from one or both adrenal glands. Prior to targeted therapy, PA results in disproportionately higher rates of cardiovascular disease compared with other forms of hypertension. The guideline-recommended treatments for PA are surgical adrenalectomy or lifelong MR antagonist therapy, largely dependent on whether the source of autonomous aldosterone secretion comes from one or both adrenal glands. Surgical adrenalectomy is highly effective in curing or improving hypertension and reducing incident cardiovascular disease among those PA patients with unilateral disease that are healthy enough and willing to undergo surgery. For the remainder of PA patients, lifelong MR antagonist therapy is the recommended treatment. However, recent studies have shown that PA patients treated with MR antagonists remain at higher risk for incident cardiovascular disease compared with patients with essential hypertension. Future studies are necessary to tailor individualized treatment approaches to patients with PA in order to optimize cardiovascular outcomes. For instance, future studies are needed to prospectively explore the role of renin as a biomarker in MR antagonist dosing schema for patients with PA. Additionally, future studies should look into expanding the indications for surgical adrenalectomy. Perhaps with severe bilateral PA where effective MR blockade cannot be achieved with more aggressive MR antagonist dosing or where patients are intolerant to higher doses of MR antagonists, surgical adrenalectomy should be considered for disease attenuation rather than disease cure (as with unilateral PA). Finally, strategies to identify earlier, milder forms of autonomous aldosterone secretion must be explored as earlier intervention in this population may have a major impact on long-term outcomes.

Compliance with Ethical Standards

Conflict of Interest Gregory L. Hundemer declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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