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Primary Aldosteronism: An Underdiagnosed and Undertreated Cause of Hypertension

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Primary aldosteronism (PA) is defined by the American College of Cardiology (ACC) and the American Heart Association (AHA) as a common form of endocrine hypertension characterized by production of aldosterone by the adrenal gland that is relatively independent of the major regulators of aldosterone secretion (angiotensin II and potassium.[1] Primary aldosteronism encompasses a group of disorders in which aldosterone levels are inappropriately high relative to sodium status.[1]

The Centers for Disease Control and Prevention (CDC) reports 108 million adults (45% of the total population) within the United States has hypertension defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg.[2] This data was extrapolated from the 2013-2016 National Health and Nutrition Examination Survey (NHANES) and applies criteria from the 2017 ACC/AHA Hypertension guidelines.[1,2]

Prior to the late 1990s, primary aldosteronism was thought to only be present in overt and spontaneous hypokalemia, which resulted in low estimated prevalence rates from 1% to 2% of hypertensive patients.[3] In recent years, a large number of studies such as the Primary Aldosteronism and Prevalence in Hypertension (PAPY) study have reported that the majority of patients with primary aldosteronism are normokalemic.[4] The PAPY study, a large prospective survey of 1,125 hypertensive patients, reported that at presentation, more than 50% of patients with adrenal-producing adenomas and 82% of those with bilateral subtypes were normokalemic.[5] There are wide variations in estimates of prevalence of primary aldosteronism depending on the characteristics of the selected population and the diagnostic method used.4 A systematic review done by Käyser et al reported the estimated prevalence of primary aldosteronism to be 3.2% to 12.7% of a total of 5,896 patients within the primary care setting across nine studies. This review also found that 1% to 29.8% of patients referred to specialists for management of their hypertension have primary aldosteronism, based on analysis of thirty studies that provided data for 36,614 patients.[3,6]

Aldosterone is a mineralocorticoid secreted by the adrenal glands as part of the renin-angiotensin-aldosterone system (RAAS).[7] Its primary role is to regulate sodium and potassium levels in the blood through activation of mineralocorticoid receptors in the cortical collecting ducts of nephrons. The site of the renal collecting duct is responsible for 2-3% (~700 mmole/day) of sodium reabsorption from the tubular lumen, predominantly via epithelial sodium (Na+) channels.[8] Activation of mineralocorticoid receptors by aldosterone causes changes in gene expression of the collecting duct to (1) code for more epithelial sodium channels (ENaC) within principal cells of the apical membrane and (2) augment activity of the sodium-potassium pump (Na+/K+ - ATPase) in the basolateral membrane.[7] This reabsorption of cationic sodium without an anion creates a lumen-negative electrical gradient which then favors the excretion of potassium and hydrogen ions. This increased excretion can lead to hypokalemia and metabolic alkalosis, with a net effect of water retention that contributes to increased intravascular volume and subsequent hypertension.[7]

Primary aldosteronism is commonly caused by an adrenal adenoma, unilateral or bilateral adrenal hyperplasia, adrenal carcinoma or inherited conditions of familial hyperaldosteronism.[9] If primary hyperaldosteronism is caused by an adrenal adenoma, it is referred to as Conn syndrome.[10] Hyperaldosteronism can be the result of excessive stimulation of aldosterone secretion from with-

Table 1 | Types of Primary Aldosteronism[11]

Types of Primary Aldosteronsim	Cases
Aldosterone-producing adenoma (APA)/Conn's syndrome	30%
Bilateral adrenal hyperplasia (BAH)	60%
Unilateral (primary) adrenal hyperplasia	2%
Adrenal cortex carcinoma	<1%
Renin-responsive adrenocortical adenoma	<0.1%
Familial Hyperaldosteronism (FH)	
Type 1—Glucocorticoid-remediable aldosteroism	<1%
Type 2—Familial occurrence of adenoma or hyperplasia	<6%
Type 3—KCNJ5 Mutation	<1%
Type 4—CACNA1H Mutation	<0.1%

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in the adrenal gland, classified as primary aldosteronism, or the result of secondary causes. Secondary aldosteronism results from an appropriate adrenal response to overstimulation of the zona glomerulosa, the outmost layer of the adrenal cortex, usually by the renin-angiotensin system. Classifying the type of primary aldosteronism is necessary to determine the appropriate course of therapy.[10]

Clinical Presentation

Primary aldosteronism usually presents with nonspecific symptoms and many patients are asymptomatic.[10] The primary sign of hyperaldosteronism is moderate to severe high blood pressure that is resistant to medication therapy with conventional antihypertensives. This is due to a lack of mineralocorticoid receptor blockade to inhibit the direct hypertensive effects of aldosterone.[10] Hypertension secondary to primary aldosteronism may or may not be associated with hypokalemia depending on severity of the disease.[9] The Endocrine Society guidelines state an estimated 9% to 37% of patients with primary aldosteronism have hypokalemia defined as serum potassium < 3.5 mmol/L. This infers that the majority of patients with primary aldosteronism present as normokalaemic, with hypokalemia only present in prolonged or severe hyperaldosteronism.[9] If hyperaldosteronism has progressed, patients may experience paresthesia, muscle aches/stiffness, nausea/vomiting, heart palpitations, breathing difficulties, and/or mood disorders due to severe hypertension and low potassium levels.

Primary hyperaldosteronism is currently underdiagnosed for several reasons.[4] The diagnosis is based on the presence of low or undetectable plasma renin levels and inappropriate high secretion of aldosterone relative to sodium status.[4] Use of plasma aldosterone concentration in isolation is not recommended due to a high variability of each individually based on posture, time of day, current medications, recent dietary salt intake, and patient characteristics (menstruation, age).[9] Likewise, an abnormal plasma renin concentration would be nonspecific to primary aldosteronism as many hormones can cause dysregulation of the renin-angiotensin-aldosterone system (RAAS). The Endocrine Society guidelines recommend the use of an aldosterone-to-renin ratio (ARR) as an initial screening test in patients listed in **Table 1** to avoid this variability and lack of specificity with isolation tests.[9]

The ARR is a ratio of plasma aldosterone concentration (PAC) to either plasma renin activity (PRA) or direct active renin concentration (DRC).[9] The DRC assay is preferred at many centers because it performs reasonably well in patients with primary aldosteronism, it is cheaper, nonradioactive, requires less manpower due to its ability to be automated, and allows for samples to be handled at room temperature.[4] Although the ARR is less variable when compared to testing aldosterone or renin in isolation, the PRA assay and DRC assay may cause the ARR to become falsely elevated in the presence of low renin levels.[4] For this reason, the Endocrine Society guidelines recommend confirmatory testing after a positive ARR test result.[9]

The oral sodium loading test (OSLT), the saline infusion test (SIT), the captopril challenge test (CCT) and the fludrocortisone suppression test (FST) have been proposed to assess for false-positive ARR values.[4] These tests are used to determine if an elevated plasma aldosterone concentration is independent of the renin-angiotensin-aldosterone system (RAAS) through alteration of sodium status. This implies that if an aldosterone level does not decrease in response to increased plasma sodium concentration, the patient is thought not to have primary aldosteronism. The confirmation tests are less accurate in terms of their positive predictive value, as many patients with primary aldosteronism, particularly with aldosterone-producing adenomas (ADA) were found to have aldosterone levels that were responsive to plasma angiotensin II concentration. This suppression of plasma aldosterone concentration in patients with curable ADA occurs after blunting angiotensin II with saline infusion or captopril administration.[4]

Table 2 | When to Consider Testing Aldosterone-to-Renin Ratio (ARR) in Hypertensive Patients[4,9]

Sustained blood pressure > 150/100 mmHg on each of three measures obtained on different days
Blood pressure > 140/90 mmHg resistant to three conventional antihypertensive drugs to include a diuretic
Four or more antihypertensive drugs required to control blood pressure to < 140/90 mmHg
Spontaneous hypokalemia (K+ < 3.5 mmol/L)
Diuretic-induced hypokalemia (K+ < 3.0 mmol/L)
Adrenal incidentaloma defined as an adrenal mass detected incidentally through imaging
Obstructive sleep apnea
Family history of early onset hypertension
Family history of cerebrovascular accident at < 40 years old
First-degree relative diagnosed with primary aldosteronism
Unexplained atrial fibrillation

Each test has its strengths and limitations. Although it is widely used and thought to be reliable, SIT is contraindicated in patients with renal insufficiency or congestive heart failure (CHF) which limits its use.[12] The captopril challenge test (CCT) is generally less expensive and can be done in an outpatient setting, however the 'correct' way to perform this test regarding the dose and intervals to collect blood samples remains controversial.[12] The FST is considered the gold standard for primary aldosteronism, as it mimics the mineralocorticoid effects of aldosterone.[13] The OSLT relies on a patient's ability to collect a 24-hour urine sample, as urinary aldosterone is measured to confirm suppression. This limits the accuracy of the test as it relies on the patient's ability to adhere to the protocol.[13] A recent meta-analysis done by Wu et al found that CCT, SIT and FST provided high accuracy in primary aldosteronism confirmation, but were unable to identify eligible studies to demonstrate accuracy of OSLT. [12]

If a patient is diagnosed with primary aldosteronism, it is important to classify the disease based on subtype to identify candidates for unilateral adrenalectomy.[4] A computed tomography (CT) imaging test is recommended by the Endocrine Society guidelines in all patients with primary aldosteronism to exclude an aldosterone-producing carcinoma, and to identify the vein responsible for adrenal drainage.[9] It is not recommended to rely solely on imaging to refer patients to surgery due to incongruent diagnoses between patients who underwent CT imaging and subsequently underwent adrenal venous sampling (AVS) on a prospective cohort of 203 patients done by Young et al.14 The authors found that CT imaging did not identify 21.7% of cases with unilateral disease, and incorrectly diagnosed 24.7% of patients with unilateral masses when a true diagnoses was bilateral or contralateral disease.[14] Due to this lack of reliability of CT imaging for distinguishing between unilateral and bilateral disease, adrenal venous

sampling (AVS) is a mainstay in differential diagnosis.[4] The procedure of AVS is expensive and not without risk, with a 0.7% chance of adrenal vein rupture.4 For this reason, AVS is not recommended by the Endocrine Society guidelines until the patient has underwent confirmation testing for primary aldosteronism to rule out a false-positive ARR.[9]

Comorbid Conditions

Metabolic Syndrome

Normal human physiological pH is 7.35 to 7.45.[15] A decrease in pH below 7.35 is labeled as acidosis, while an increase to greater than 7.45 is called alkalosis. Metabolic alkalosis refers to a disease state with an elevated physiological pH secondary to a metabolic disorder.[15] The American Heart Association (AHA) defines metabolic syndrome as the presence of three or more of the following criteria; waist circumference > 40 inches in men or > 35 inches in women, triglycerides ≥150 mg/dL, HDL < 40 mg/dL in men or < 50 mg/dL in women, blood pressure > 130/85 mmHg, and fasting glucose ≥100 mg/dL.[16]

Enhanced urinary excretion of hydrogen ions in addition to kaliuresis may contribute to the likelihood of patients with primary aldosteronism dveloping metabolic alkalosis.[16] However, the primary proposed mechanism by Fallo and colleagues are the direct effects of aldosterone on tissues and organs outside of the kidneys to cause decreased insulin sensitivity. The article infers that aldosterone acts on the insulin receptor gene within adipocytes to cause downregulation of insulin receptors, which leads to dysfunction of white adipose tissue. Studies have found that white adipose tissue has effects on the autocrine, paracrine and endocrine systems and express many proteins and hormones that contribute to metabolic syndrome.[16]

Renal Insufficiency

Normal protein excretion in the urine is < 150 mg every 24 hours.[17] Significant proteinuria is commonly used as a biomarker for early renal damage based on the assumption that increased protein in the urine indicates a malfunction in glomerular filtration.[17] Multiple studies have found earlier onset and more severe kidney damage in patients with primary aldosteronism compared to essential hypertension. One study proposed the correlation was due to mineralocorticoid receptor upregulation in the kidneys based on biopsies of patients with severe proteinuria. Other studies have found increased inflammatory biomarkers such as macrophage-chemoattractant protein 1 and transforming growth factor β1, osteopontin, interleukin 1 (IL1), and interleukin 6 (IL6) in the presence of high plasma aldosterone concentrations which would lead to detrimental effects on the kidneys.[17]

Treatment

Clinical practice guidelines developed over the past decade by several countries and international organizations have published inconsistent evidence and statements on the appropriate treatment of primary aldosteronism.[18] The Endocrine Society, and the Canadian Hypertension Education Program are the only organizations identified in one study by Wu et al to have published guidelines based on good methodology regarding endocrine hypertension and primary aldosteronism overall. The Appraisal of Guidelines for Research and Evaluation Instrument (AGREE-II) and Institute of Medicine (IOM) instrument were used to evaluate the methodological quality of the guidelines. Both guidelines recommend laparoscopic adrenalectomy in patients with unilateral disease or mineralocorticoid receptor blockade with spironolactone as first-line therapy in non-surgical candidates. Other potential agents are eplerenone, or medication in the epithelial sodium channel blockers class, amiloride or triamterene. These medications are recommended for treatment in primary aldosteronism based on their ability to decrease effects of aldosterone at the level of the kidneys. Mineralocorticoid receptor antagonists prevent aldosterone from binding to the mineralocorticoid receptor in the nephron tubules which prevents the subsequent upregulation of sodium channels. Amiloride and triamterene are direct sodium channel blockers and so prevent increased sodium reabsorption from the excess sodium channels. Spironolactone is recommended as the gold standard for non-surgical candidates based on a multitude of studies that have demonstrated cardiovascular morbidity and mortality in primary aldosteronism.[18]

Goals of medical therapy for treatment of primary aldosteronism differ from essential hypertension by focusing more on reversal of cardiovascular morbidity through reduction of excess aldosterone and normalization of potassium levels in patients with secondary hypokalemia.[9] The course of therapy depends on the underlying cause of hyperaldosteronism.[16] Patients with unilateral disease are recommended to undergo laparoscopic adrenalectomy with the additional goal of either eliminating the need for medication or reducing medication-related side effects.[9]

Laparoscopic adrenalectomy cures primary aldosteronism and resolves or improves arterial hypertension in most cases, with significantly better outcomes in early diagnosis.[6] Collective evidence also demonstrates that patients with unilateral primary aldosterone who qualify for surgical removal of the adrenal gland have better outcomes than patients with bilateral disease treated with mineralocorticoid receptor antagonists (MRAs).[15] Lechner et al proposed that by removing the source of mineralocorticoid excess, and the often accompanying glucocorticoid excess, might be an explanation for the observation of slightly better outcomes.[14] The authors also proposed three major reasons for the discrepancy between cardiovascular outcomes in patients who undergo surgical therapy compared to patients treated with MRAs. First is that no measurable treatment goal for adequate

Table 3 | Drugs That Affect the Aldosterone-to-Renin Ratio[4]

Drug Class	PAC[a]	Renin	ARR[b]
Beta-Blockers*	↓	↓↓	↑
Central α-2 agonists	↓	↓↓	↑
NSAIDs[c]	↓	↓↓	↑
Loop Diuretics**	↑	↑↑	↓
Thiazide Diuretics	↑	↑↑	↓
ACE[d] Inhibitors***	↓	↑↑	↓
ARBs[e]	↓	↑↑	↓
Calcium Channel Blockers	↓ or ↔	↔	↓

[a]Plasma aldosterone concentration; [b]Aldosterone-to-renin ratio; [c]Non-steroidal anti-inflammatory drugs; [d]Angiotensin converting enzyme; [e]Angiotensin receptor blockers
*Beta blockers reduce renin levels to a greater degree than aldosterone levels, and thus can lead to an elevated ARR.[4] The Endocrine Society recommends discontinuation of beta-blockers for at least 4 weeks prior to the PRA or DRC assay to avoid false positives.[9]
**Diuretics should be held for at least 3-4 weeks before to reduce the risk for false negatives due to their effects on increased renin secretion.[4]
***Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) should also be discontinued for 3-4 weeks before ARR because they decrease aldosterone secretion which may lead to a false negative ARR.[4]

aldosterone blockade has been established.[14] Second, adverse effects of MRAs, particularly the antiandrogenic effects of spironolactone, often limit patient compliance.[14] The third reason mentioned is due to less extensive recommendations for drug dosing compared to other disease states such as heart failure.[14]

Clinical Trials

Parthasarathy et al.

A double-blind, randomized controlled trial conducted by Parthasarathy et al assessed the antihypertensive effect of eplerenone compared to spironolactone in hypertensive patients with primary aldosteronism.[21] Eligible patients had to be at least eighteen years of age with hypertension defined as diastolic blood pressure 90-120mmHg with systolic blood pressure <200mmHg, potassium levels of 3.0-5.0mmol/L and a diagnosis of primary aldosteronism.[21] A total of 141 patients were enrolled in the study with 70 patients receiving eplerenone and 71 patients receiving spironolactone.[21] Within the eplerenone group, three participants did not take therapy, 19 remained on 100mg, 18 received 200mg and 28 received 300mg. In the spironolactone group, one participant was not taking therapy, while 22 received 75mg, 22 received 150mg and 24 received 225mg daily. The baseline demographics were similar between groups with regard to age (mean 53 years old), blood pressure, body mass index (BMI), creatinine, sodium, potassium, plasma renin activity and plasma aldosterone concentration.

The primary efficacy endpoint was the antihypertensive effect of eplerenone versus spironolactone to establish non-inferiority of eplerenone in the average change of seated diastolic blood pressure at baseline to 16 weeks.[21] A decrease in baseline diastolic blood pressure was observed in both groups with –5.6 ± 1.3 mmHg for eplerenone and –12.5 ± 1.3 mmHg for spironolactone.[21] The difference in blood pressure lowering between groups was –6.9 mmHg (95% CI –10.6 to –3.3) with p value < 0.001 which indicates statistical significance of spironolactone lowering blood pressure to a greater extent.[21] Noninferiority of eplerenone when compared to spironolactone was not established as the 95% lower confidence limit for the difference between treatment groups was –10.0 mmHg.[21]

Changes in the renin-angiotensin-aldosterone-system (RAAS) and sex hormones were assessed in the secondary analysis.[21] The increase in plasma renin activity from baseline was significantly greater in the spironolactone group than the eplerenone group at 214.9% increase and 86.2% increase respectively.[21] Both groups had increased plasma aldosterone concentration with a 73.3% increase in the eplerenone group, and a higher increase of 112.2% in the spironolactone group. As a result, the authors concluded that the antihypertensive effect of spironolactone is greater when directly compared to eplerenone.[21]

PATHWAY-2 Substudy

Mineralocorticoid receptor antagonists (MRAs) and epithelial sodium channel (ENaC) blockers are both classified as potassium-sparing diuretics. The Endocrine Society guidelines regard amiloride as less efficacious than spironolactone, without the beneficial effects of endothelial function in treatment of primary aldosteronism but notes its lack of sex steroid-related adverse effects as

Table 4 | Pharmacokinetic Comparison of Potassium-Sparing Diuretics[12,13,16,18]

	Mineralocorticoid Receptor Antagonists		Epithelial Sodium Channel Blockers	
Parameter	**Spironolactone**	**Eplerenone**	**Amiloride**	**Triamterene**
Cardiovascular FDA Indication	Primary Aldosteronism, Hypertension, Heart Failure	Hypertension Heart Failure	Hypertension	Edema
Dosing	12.5-25mg once daily Max dose: 400mg/day	25mg twice daily Max dose: 300mg/day	5mg once daily Max dose: 30mg BID	HTN: 50-100mg/day Max dose: 300mg/day
Renal Dose Adjustments	eGFR 30-50mL/min/1.73m2: 12.5mg starting dose Max dose: 25mg/day eGFR < 30mL/min/1.73m2: avoid use	CrCl < 50mL/min: contraindicated	CrCl 10-50mL/min: 50% normal dose ≥ 65 years old with CrCl < 30mL/min: avoid use	CrCl < 50mL/min: avoid use ≥ 65 years old with CrCl < 30mL/min: avoid use
Bioavailability	90% (increased with high-fat meal)	69%	30-90%	30-70%
Peak Effect	2.6-4.3 hours	~1.5-2 hours; may take up to 4 weeks for full antihypertensive effects	3-4 hours	~3 hours
Half-Life	1.4 hours	3-6 hours	6-9 hours	1-2 hours
Protein Binding	> 90%	~50%; primarily to alpha1-acid glycoproteins	Minimal	67%
Metabolism	First-pass metabolism into active metabolites canrenone, 7-alpha-spirolactone, and 6-beta-hydroxy-7-alpha	CYP3A4 to inactive metabolites	Does not undergo hepatic metabolism	CYP1A2 to active metabolite p-hydroxy-triamterene ester
Elimination	Urine (primarily as metabolites) Feces	Urine (~67%); Feces (~32%)	Urine (~50%); Feces (~40%)	Urine (21-50%)

an advantage.[9] PATHWAY-2 was a randomized, double-blind, cross-over trial that compared spironolactone 25-50 mg, bisoprolol 5-10 mg, doxazosin 4-8 mg and placebo in the setting of treatment-resistant hypertension.[13] A sub-study of the PATHWAY-2 trial assessed the effect of amiloride 10-20 mg once daily on clinic systolic blood pressure during an optional 6-12 week open-label run out phase.[14] Of the patients who had taken spironolactone in the PATHWAY-2 trial, 146 enrolled in sub-study 3 to take amiloride. The baseline characteristics of patients within sub-study 3 had similar blood pressure, kidney function, and urinary sodium concentrations at about 150 mmol/day. The primary outcome was change in clinic systolic blood pressure from baseline to the end of 6 weeks with amiloride 10 mg, or 12 weeks with amiloride 20 mg. Results at 6 weeks demonstrated that amiloride 10 mg had a similar blood pressure result to the patient's previous blood pressure on spironolactone. The reductions in clinic systolic blood pressure from baseline to 6 weeks were 20.4 mmHg (95% CI 18.3-22.5) with amiloride 10 mg and 18.3 mmHg (95% CI 16.2 -20.5) with spironolactone 25mg.

There were 47 patients enrolled in sub-study 3 who did not achieve blood pressure control at 6 weeks of amiloride 10 mg. For this population, they were given amiloride 20 mg from week 6 to 12. Spironolactone dose was also increased from 25 mg to 50 mg. There was a positive correlation between the systolic blood pressure lowering effect of both drugs.[14]

Fourkiotis et al

A prospective cohort conducted by Fourkiotis et al assessed the renoprotective effects of spironolactone and eplerenone over the course of three years in patients with primary aldosteronism, and the effect of MRA treatment initiation on urinary albumin excretion and estimated glomerular filtration rate (eGFR). The study was divided into two cohorts; newly diagnosed primary aldosteronism patients, and previously diagnosed patients on medical therapy.[14] This study is particularly interesting because clinical and experimental studies have demonstrated that elevated plasma aldosterone concentrations have harmful effects on the kidneys independent of blood pressure control. The theory behind this is that oxidative stress on the vasculature caused by aldosterone itself leads to fibrosis and damage to the epithelial lining.[14]

Cohort one had a sample size of 29 newly diagnosed patients who were examined for aldosterone levels, blood pressure, eGFR, creatinine, and urinary albumin-to-creatinine (UAE/Ucrea) ratio prior to treatment initiation, and one year thereafter.[14] Patients were further subdivided into those who received adrenalectomy vs spironolactone 55.0 ± 7.3 mg/day. The average eGFR decreased by –10.8 mL/min/1.73m2 ($P < 0.05$) and the UAE/Ucrea ratio decreased by –69.3 mg/g ($P < 0.001$) both indicative of statistical significance. Additionally, aldosterone levels decreased significantly from pretreatment (264.1 ± 49.8 ng/L) to follow up (43.7 ± 17.0 ng/L) with a p value < 0.01. The author's proposed mechanism for this response is the presence of aldosterone-induced glomerular hyperfiltration prior to therapy. Treatment with adrenalectomy or spironolactone causes a reduction in plasma aldosterone concentration and thus a return of normal glomerular function.[14]

The second cohort assessed the same renal biomarkers as cohort one, but in patients diagnosed with primary aldosteronism at an average 5.3 years prior to the study already on medical therapy.[14] Cohort two included 188 patients with follow up at 1.5 and 3 years. The majority of patients in this group (76.6%) were surgical candidates who underwent adrenalectomy. Within the remainder of patients (65) received spironolactone 63.5 ± 5.8 mg/day, and 18 patients eplerenone 88.2 ± 1.0 mg/day. The average eGFR remained stable at 1.5 years (67.5 ± 1.9 mL/min/1.73m2) and 3 years (68.7 ± 1.8 mL/min/1.73m2).[14]

Adverse Effects of Therapy

Albeit a rare consequence of therapy, the risk for hyperkalemia exists for all primary aldosteronism treatment options, particularly after unilateral adrenalectomy.[25] The reasons for prolonged suppression of aldosterone following unilateral adrenalectomy remain unclear.26 Elevated serum potassium > 5.5 mmol/L is considered critically high, and can lead to life-threatening cardiac arrhythmias. Regarding therapy with spironolactone or eplerenone, the risk for hyperkalemia is more pronounced in normokalaemia patients with impaired renal function as increased sodium excretion may lead to relatively high intracellular potassium. The epithelial sodium channel blockers (ENaC) amiloride and triamterene have a higher incidence of hyperkalemia compared to MRAs with 10% of patients receiving amiloride experiencing this adverse effect.[26]

Clinical Implications

If hypertension secondary to hyperaldosteronism is not detected, or inappropriately treated with antihypertensives without mineralocorticoid receptor blockade, this can lead to an unaddressed high risk of cardiovascular/renal complications, including arrythmias, myocardial infarction, stroke, chronic kidney disease and death.

A limitation to the study by Parthasarathy et al is its use of surrogate endpoints (blood pressure and plasma aldosterone level) instead of long-term clinical endpoints such as effects on the cardiovascular system (left ventricular dimensions, myocardial fibrosis, and endothelial function), and cardiovascular/renal complications (arrythmias, chronic kidney disease, myocardial infarction, stroke).[9] Another limitation was the lack of a dose equivalence curve with titration of spironolactone and eplerenone.[9] Eplerenone has a short half-life of ~3-6 hours.[9] While the half-life of spironolactone is 1.5 hours, its active metabolite canrenone has a half-life of 16.5 hours.[9] It is recommended by the Endocrine Society guidelines to divide the eplerenone dose into two doses. This trial dosed eplerenone once daily which may have led to a disadvantage in the eplerenone treatment group.[9] Lastly, this study excluded patients who could not be titrated down from antihypertensives which may encompass a relatively large subpopulation of patients with primary aldosteronism which and limit generalizability of this study.[9]

Mineralocorticoid receptor antagonists (MRAs), particularly spironolactone, have demonstrated efficacy as potential breakthrough therapy for resistant hypertension in trials such as the PATHWAY-2 study.[20] The study enrolled patients with resistant hypertension despite treatment with maximally tolerated doses of three antihypertensive medications (to include an ACE inhibitor plus a calcium channel blocker plus a thiazide/thiazide-like diuretic) for at least three months. A comparison of add-on therapy with spironolactone 25-50 mg, bisoprolol 5-10 mg or doxazosin 4 -8 mg concluded that spironolactone was superior to doxazosin and bisoprolol at reducing blood pressure. The change from baseline was -14.4 mmHg (-15.6 to -13.1 mmHg) in spironolactone add-on therapy, compared to an average -9.1 mmHg decrease wit

doxazosin and – 8.4 mmHg decrease in the bisoprolol group. According to the authors, spironolactone was the most effective treatment for resistant hypertension and should be incorporated into future guidelines for the condition.[20]

The study by Fourkiotis and colleagues did not report an a priori power to determine the sample size needed to reject the null hypothesis appropriately. Other than classification based on surgical and nonsurgical candidates, there was no other mention of subtype classification or etiology of primary aldosteronism. A prospective cohort is not an ideal study design when compared to a randomized controlled trial due to potential confounding factors. Although this was a multi-center study population of 29 patients is considerably small for the cohort involving patients with incidence exposure to spironolactone. Eplerenone was not included in the first cohort, so may not be able to extrapolate findings to patients treated with this medication. Cohort one also did not include elderly patients > 66 years old which limits external validity to these patients in practice. The second cohort had follow-up times of 1.5 and 3 years which is a relatively short time period considering lifelong therapy with MRAs. There was also no data for renal biomarkers at baseline or prior to treatment initiation for the second study. This may have been beneficial to assess for severity of disease and pre-existing renal impairment.

Conclusion

Primary aldosteronism is a commonly undetected cause of secondary hypertension with higher rates of cardiovascular morbidity/mortality and target organ damage than patients with similar characteristics and blood pressure control. Some subtypes of primary aldosteronism allow for surgical intervention which has a high rate of clinical cure. This is why it is of utmost importance to screen patients with hypertension for potential indications to test for primary aldosteronism.

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Table 3 | Pharmacokinetic Comparison of Potassium-Sparing Diuretics[12,13,16,18]

Trial	Study Design	Primary Outcome	Intervention	Results
Parthasarathy et al.	RCT[a]	Change in seated DBP[b] from baseline to 16 weeks of therapy.	Spironolactone 75-225mg daily (n = 71) Eplerenone 100-300mg daily (n = 70)	DBP: decrease was lower in eplerenone (-5.6 ± 1.3 mmHg) than spironolactone (-12.5 ± 1.3 mmHg) difference between groups was -6.9 mmHg (-10.6, -3.3); P < 0.001.
PATHWAY-2; Substudy 2	RCT	Changes in SVR[c] and TFV[d] from baseline to 12 weeks of treatment.	Spironolactone 25-50mg daily Amiloride 10-20mg daily	SVR: Amiloride 10 mg reduced clinic systolic blood pressure by 20.4 mmHg (95% CI 18.3–22.5), compared with a reduction of 18.3 mmHg (16.2–20·5) with spironolactone 25 mg. TFV: Spironolactone reduced thoracic fluid content by 6.8% from baseline (95% CI 4.0 to 8.8; P < 0.0001) but was not reduced with amiloride
Fourkiotis et al.	Prospective Cohort	**Cohort 1** Change in eGFR, UAE/Ucrea ratio[e], blood pressure and serum creatinine from pretreatments to 1 year after treatment. **Cohort 2** Change in eGFR, UAE/Ucrea ratio, blood pressure and serum creatinine at 1.5 years and 3 years in patients previously on medication therapy with spironolactone, eplerenone or other antihypertensives.	**Cohort 1 (n = 29)** Adrenalectomy (n = 18) Spironolactone 55.0±7.3mg/day (n = 11) **Cohort 2 (n = 188)** Spironolactone 63.5 ± 5.8 mg/day (n = 65) Eplerenone 88.2 ± 11.0mg/day (n = 18) Other Antihypertensives; 33.3% diuretics, 28.6% beta-blockers, 33.3% alpha-blockers, 33.3% ACE inhibitors, 33.3% Angiotensin II antagonists, and 38.1% calcium-channel blockers	**Cohort 1** eGFR: decreased by –10.8 mL/min/1.73m2; P < 0.05 UAE/Ucrea ratio: decreased by –69.3 mg/g; P < 0.001 PAC[f]: decreased by –220.4 ng/L; P < 0.01 **Cohort 2** eGFR: remained stable at 1.5 years (67.5 ± 1.9 mL/min/1.73m2) and 3 years (68.7 ± 1.8 mL/min/1.73m2) UAE/Ucrea ratio: remained stable at 1.5 years (36.8 ± 6.5 mg/g) and 3 years (33.0 ± 8.6 mg/g) No. of antihypertensive drugs: increased significantly in patients who did not take eplerenone or spironolactone and did not undergo adrenalectomy: 1.5 years (2.3 ± 0.6) and 3 years (2.4 ± 0.6); P < 0.05

[a]Randomized controlled trial; [b]Diastolic blood pressure; [c]Systemic vascular resistance; [d]Thoracic fluid volume; [e]Urinary albumin to creatinine ratio; [f]Plasma aldosterone concentration

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New Indication: First-line treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score ≥50%), as determined by an FDA-approved test. Patients must either have metastatic or locally advanced tumors that are not candidates for surgical resection or definitive chemoradiation, and the tumors must not have EGFR, ALK or ROS1 aberrations.

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