Hyperaldosteronism: How Current Concepts Are Transforming the Diagnostic and Therapeutic Paradigm

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Abbreviations

PA=Primary Hyperaldosteronism
CVD=Cardiovascular Disease
PAPY=Primary Aldosteronism Prevalence in Hypertension
APA=Aldosterone-Producing Adenoma
BAH=Bilateral Adrenal Hyperplasia
ARR=Aldosterone Renin Ratio
AF=Atrial Fibrillation
OSA=Obstructive Sleep Apnea
OR=Odds Ratio
AHI=Apnea Hypopnea Index
ABP=Ambulatory Blood Pressure
AVS=Adrenal Vein Sampling
CT=Computerized Tomography
MRI=Magnetic Resonance Imaging
SIT=Sodium Infusion Test
FST=Fludrocortisone Suppression Test
CCT=Captopril Challenge Test
PAC=Plasma Aldosterone Concentration
PRA=Plasma Renin Activity
MRA=Mineralocorticoid Receptor Antagonist
MR=Mineralocorticoid Receptor
Abstract

Nearly seven decades have elapsed since the clinical and biochemical features of Primary Hyperaldosteronism (PA) were described by Conn. PA is now widely recognized as the most common form of secondary hypertension. PA has a strong correlation with cardiovascular disease and failure to recognize and/or properly diagnose this condition has profound health consequences. With proper identification and management, PA has the potential to be surgically cured in a proportion of affected individuals. The diagnostic pursuit for PA is not a simplistic endeavor, particularly since an enhanced understanding of the disease process is continually redefining the diagnostic and treatment algorithm. These new concepts have emerged in all areas of this clinical condition, including identification, diagnosis, and treatment. Here, we review the recent advances in this field and summarize the impact these advances have on both diagnostic and therapeutic modalities.

Introduction

Hypertension is the strongest modifiable risk factor for cardiovascular disease worldwide. Despite increasing disease awareness, the prevalence of uncontrolled hypertension remains high (1). Recently, The Lancet Commission on Arterial Hypertension identified key actions to improve the management of blood pressure globally (2). Among the key steps proposed to combat elevated blood pressure was better identification of individuals with secondary hypertension. The hope is that a more streamlined evaluation for secondary hypertension would
Primary hyperaldosteronism (PA) is one of the most common forms of secondary hypertension. Although the prevalence of PA varies greatly depending on the study population, the prevalence of PA may be as high as 22% among individuals with resistant hypertension (3). Moreover, individuals with PA share a strikingly, inordinate burden of cardiovascular disease compared to individuals with essential hypertension (4-6). Compared to individuals with essential hypertension, the presence of hyperaldosteronism increased the risk of myocardial infarction, stroke, and atrial fibrillation on the magnitude of 4-fold, 6-fold, and 12-fold, respectively (4). Improved identification of individuals with PA is critical given the strong correlation between aldosterone and cardiovascular disease.

The evaluation for PA is not a simplistic endeavor. Clinical practice guidelines and algorithms for the evaluation and management in PA have been established in an effort to standardize the diagnostic pursuit and optimize disease management. A general assessment of the validity and applicability of clinical guidelines for PA demonstrate incongruity in diagnostic approaches and considerable challenges with ease of implementation (7). These issues often result in clinical uncertainty, which can delay, retard, or even halt the diagnostic work-up for PA in the clinical setting. This article highlights some of the evolving concepts in PA that are enhancing our understanding of the clinical entity and transforming the current diagnostic and therapeutic models of care.
Serum Potassium and PA

Historically, hypokalemia has been considered an essential component of the clinical presentation of individuals with PA. Early clinical studies discounted hypokalemia as the *conditio sine qua non* for PA. For instance, The PAPY (Primary Aldosteronism Prevalence in Hypertension) study was a prospective study of 1180 consecutive patients with newly diagnosed hypertension who were evaluated for PA using a rigorous protocol (8). In this cohort, only 48% of the participants who were found to have an aldosterone-producing adenomas (APA) had concomitant spontaneous hypokalemia. The presence of hypokalemia does suggest a more florid clinical phenotype PA and could be a useful tool in subtype classification and predicting surgical response to adrenalectomy. In the PAPY study, the prevalence of hypokalemia was significantly higher in APA compared to bilateral adrenal hyperplasia (BAH) [49% vs 16%]. The patients with hypokalemia and APA tended to have higher ARR (aldosterone to renin ratio) values, which generally favor a more complete clinical response to surgical adrenalectomy. Taken together, these findings provide compelling data that hypokalemia is not a consistent hallmark of PA, but rather, is a crude tool to differentiate APA from BAH and predict response to surgical adrenalectomy in APA.

A more recent study showed contradictory observations regarding the prevalence of hypokalemia in PA compared to early observations. Burrello et al examined the prevalence of hypokalemia and PA in 5100 patients referred to a tertiary hypertension unit and observed a graded relationship between serum potassium and prevalence of PA (9). Among patients with spontaneous hypokalemia, the prevalence of PA increased from 21.8% in patients with
potassium of 3.5 to 3.6 mmol/L up to 88.5% in patients with potassium concentrations <2.5 mmol/L. In fact, hypokalemic hypertension was the more common phenotype in this cohort of patients referred for hypertensive care. Since the available data demonstrate wide variation in the prevalence of hypokalemia in PA, hypokalemia likely has inadequate sensitivity and specificity to serve as a valuable tool for case detection of PA.

The presence of hypokalemia in the setting of PA may have value that transcends disease identification and subtype classification. A growing body of evidence has demonstrated that hypokalemia in the setting of PA is associated with a more profound cardiovascular and metabolic morbidity and mortality. In the aforementioned study by Burrello et al, the prevalence of cardiovascular events were higher in patients with hypokalemia compared to normokalemia (10.7% versus 6.3%, p<0.001). Specifically, patients with hypokalemia displayed a higher risk of arrhythmias (3.4% versus 1.8%, p=0.006), heart failure (1.0% versus 0.4%, p=0.032), and stroke (3.3% versus 1.1%, p<0.001). Lastly, patients with hypokalemia demonstrated a higher prevalence of CKD (8.6% versus 3.2%, p<0.001). Future studies are necessary to further elucidate the association between hypokalemia and PA with increased cardiovascular risk and target end-organ damage.

**New Insights into Disease Prevalence**

A recently released cross-sectional analysis has provided contemporary insights in the prevalence of PA, while also redefining our conceptual understanding of renin-independent aldosterone production as it applies to hypertension (Figure 1) (10). This study examined the
prevalence of PA among more than 1000 patients from four geographically diverse US centers. Two thirds of patients had adequate suppression of renin to assess renin-independent aldosterone production. The prevalence of primary aldosteronism among patients with normotension, stage 1 hypertension, stage 2 hypertension, and resistant hypertension was 11%, 16%, 22%, and 22% respectively. Besides demonstrating that PA is a more prevalent condition than previously thought (even among normotensive and normokalemic individuals), the authors described a spectrum of renin-independent aldosterone production that paralleled the severity of hypertension. Based on these results, it is apparent that our perception that PA is a rare disease needs to be reconsidered, since even among normotensive individuals the prevalence of renin-independent hyperaldosteronism was high. Importantly, the clinical entity of PA may represent a more clinically apparent and florid phase of a seemingly emerging spectrum of renin-independent, aldosterone-mediated hypertension.

**Emerging Associations Between PA and Clinical Diseases**

New associations between PA and clinical disease entities are emerging, particularly atrial fibrillation (AF) and obstructive sleep apnea (OSA). A strong association between PA and atrial fibrillation (AF) has been observed in the past decade. Milliez et al recently examined the rate of cardiovascular events in patients with PA and observed a 12-fold increased risk of AF in PA compared with essential hypertension (EH) [PA 7.3 EH 0.6, OR 12.1, p < 0.0001] (11). These results were confirmed by Monticone et al who performed a systematic review and meta-analysis of 31 studies to examine the rates of cardiovascular events among participants with PA compared
with essential hypertension (12). The risk of AF was 3.52, 95% CI 2.06-5.99 in the participants with PA compared with essential hypertension.

Interestingly, the completeness of aldosterone blockade in PA may impact the future risk of developing AF. Hundemer et al investigated whether mineralocorticoid receptor (MR) antagonist therapy or adrenalectomy in PA influence the risk for incident AF (13). PA patients who were treated with surgical adrenalectomy had no statistically significant difference in risk for incident AF compared with essential HTN. Despite similar blood pressure control, patients with PA treated with MR antagonist had a higher risk for incident AF compared with essential hypertension, when the renin levels remained suppressed on MR blockade. Conversely, patients with PA who were treated with MR antagonists and experienced an increase in renin or had surgical adrenalectomy had no statistically significant difference in risk for incident AF compared with patients with essential HTN. Similarly, Rossi et al recently published results showing that adrenalectomy significantly lowered incident AF in patients with PA (14). After a median follow-up of 11.8 years, medically treated PA showed a lower AF-free survival than PA patients treated surgically. Taken together, individuals with apparently unprovoked AF should be screened for PA and individuals with PA should undergo appropriate therapy to reduce the risk of incident AF.

The association between aldosterone and OSA is strengthening and plausible mechanisms responsible for the association are under investigation. The association between symptoms of OSA and the presence of PA was evaluated by Calhoun et al (15). Subjects at high risk of OSA were almost two times more likely to have PA (36% vs 19%). The frequency of PA in OSA
patients was evaluated in the study of diMurro et al (16). The authors included 325 consecutive patients with newly diagnosed hypertension. 34% of the patients with OSA were also diagnosed with PA and BAH was identified as the most common sub-type of PA. In the Resist-POL study, 204 consecutive patients with resistant hypertension were evaluated (17). OSA was marginally, but significantly higher in individuals with PA than without PA. Moderate-to-severe OSA tended to occur more frequently in patients with PA compared to patients without PA. Additionally, comorbid OSA and PA was associated with more pronounced target organ damage. It has been postulated that aldosterone worsens OSA by promoting fluid accumulation in the upper airway resulting in airway resistance (18). In summary, there appears to be a strong, bidirectional association between OSA and PA that is mediated by aldosterone.

Clinical evidence has established strong associations between aldosterone excess, resistant hypertension, and OSA (19). Moreover, therapies directed at aldosterone excess in OSA and resistant hypertension appear to have profound clinical benefits. For instance, Yang et al examined the effects of spironolactone on patients with resistant hypertension (not confirmed to have PA) and OSA (20). After 12 weeks of follow-up, the apnea-hypopnea index (21.8 to 1.8, p<0.05), plasma aldosterone levels (9.8 to 2.9, p<0.05), clinic blood pressure, and ambulatory blood pressure (ABP) were reduced significantly in the treatment group compared to the control group. Similar results have been identified in patients with PA. Wolley et al recruited patients undergoing diagnostic evaluation for PA who had symptoms suggestive of OSA. The patients who had PA confirmed underwent polysomnography at baseline and at least 3 months after specific treatment for PA. Patients with aldosterone-secreting adenomas and bilateral adrenal hyperplasia were treated with surgical adrenalectomy and mineralocorticoid receptor blockade,
respectively. For the patients who were diagnosed and subsequently treated for PA, the median apnea-hypopnea index dropped from 22.5 to 12.3 (p=0.02) (21). These studies suggest a strong link between aldosterone excess, hypertension, and OSA, which can be effectively managed through aldosterone-reducing strategies.

Confirmatory Testing

Clinical practice guidelines generally favor confirmatory testing for a positive ARR (aldosterone renin ratio) prior to subtype classification (22). Confirmatory testing for PA can be performed through: oral sodium loading, saline infusion test (SIT), fludrocortisone suppression test (FST), or captopril challenge test (CCT). These tests are cumbersome, time-consuming, and guidelines provide limited insight to the preferred confirmatory test.

Confirmatory testing does not appear to be an evidence-based practice. In the recently published Aldosterone-Renin Ratio for Primary Hyperaldosteronism (AQUARR) Study, the value of confirmatory testing for the diagnosis of PA was examined (23). The study revealed three key findings that are applicable to this discussion. First, the study showed no diagnostic gain from the systematic use of the CCT over baseline ARR in a population with high prevalence of PA. Secondly, the sensitivity and specificity of ARR was validated in a population with high prevalence of PA. Lastly, ARR provided essential quantitative information in the evaluation of PA, that is to say, progressively increasing ARR values implied an exponential increase in specificity and decrease in false positive rates. Both the diagnostic odds ratio (DOR) and the positive likelihood ratio (LRP) were high (6.35 and 17.7, respectively) for ARR values above 50.
Taken together, these results imply that ARR is a highly effective screening test for PA and, even more surprising, an ARR value above 50 carried the same diagnostic power as confirmatory testing.

The Endocrine Society Guidelines for PA state that confirmatory testing can only be bypassed in patients with concomitant hypokalemia, marked suppression of renin, and plasma aldosterone concentration (PAC) greater than 20 ng/dL (22). Since hypokalemia occurs in only a minority of patients with PA, it is not surprising that only a very small percentage of patients would fulfill these criteria. Essentially, this makes confirmatory testing mandatory in the vast majority of cases. Given the poor performance of confirmatory testing in clinical studies, broad-scale application of confirmatory testing in the evaluation of PA appears misguided.

**Normal Aldosterone PA**

PA can occur in the setting of relatively normal plasma aldosterone concentrations (PAC) (21). There are a few plausible explanations for this paradoxical phenomenon. Aldosterone is secreted in a pulsative manner that generally occurs more readily in the early morning (26). If PAC samples are obtained during a latent phase, this will result in spuriously normal aldosterone levels. Normal aldosterone levels in the setting of PA also result from a strong physiologic response to high sodium intake (27). PAC levels can be normal despite a clinical phenotype of PA due to variation in aldosterone sensitivity. Age and race appears to be major determinants of sensitivity to aldosterone. Tu et al found that the effect of aldosterone on blood pressure (BP) intensified as age increased, especially in blacks (p<0.01), suggesting an increased aldosterone
sensitivity with age (28). In comparison to blacks, age-related changes in aldosterone sensitivity in whites were not statistically significant. These findings raise concern about using absolute value of PAC as an inclusion criteria for PA.

Imaging For PHA classification

The majority of guidelines on PA recommend computerized tomography (CT) or magnetic resonance imaging (MRI) as the best initial test for subtype classification in PA. These imaging modalities are an attractive option for subtype classification in PA compared to adrenal vein sampling (AVS) since they are generally safe, widely available, and can provide results expediently. Unfortunately, the diagnostic performance of cross-sectional imaging for PA demonstrates wide variation and can serve as a barrier to curative adrenalectomy in suitable candidates (29). The following section describes several pitfalls of imaging in the diagnostic evaluation of PA that require consideration.

CT and MRI have been increasingly used to detect adenomas despite numerous studies challenging the accuracy of cross-sectional imaging. In a Mayo Clinic Study, 203 patients with primary hyperaldosteronism were selected prospectively for AVS on the basis of degree of aldosterone excess, age, desire for surgical treatment, and CT findings (30). On the basis of CT findings alone, nearly 22% of patients would have inappropriately excluded from adrenalectomy. Furthermore, nearly 25% of the patients might have undergone unnecessary or inappropriate adrenalectomy. In a systematic review, Kempers et al found that CT/MRI results did not agree with AVS results in 37.8% of patients (31). More specifically, if only CT/MRI results had been
used to determine lateralization of an adrenal abnormality, inappropriate adrenalectomy would have occurred in 14.6% of patients (where AVS showed a bilateral problem), inappropriate exclusion from adrenalectomy would have occurred in 19.1% (where AVS showed unilateral secretion), and adrenalectomy on the wrong side would have occurred in 3.9% (where AVS showed aldosterone secretion on the contralateral side). In a more current study from Munich, 175 patients who underwent unilateral laparoscopic adrenalectomy for PA after CT/MRI and lateralization by AVS, CT imaging and MRI showed discordant results 39% and 41%, respectively (32). These studies highlight the dangers of using CT or MRI to both diagnose and manage PA.

Imaging may have better reliability for the diagnosis of bilateral adrenal hyperplasia rather than discrete adrenal adenomas. Lingam et al found that the adrenal glands in patients with bilateral adrenal hyperplasia (BAH) were significantly (p< 0.05) larger than those in patients with aldosterone-producing adenoma or in healthy control subjects (33). A sensitivity of 100% was achieved when a mean limb width of greater than 3 mm was used to diagnose BAH, and a specificity of 100% was achieved when the mean limb width was 5 mm or greater. In the future, broad application of limb width measurement of the adrenal glands may be reliable and accurate tool for the diagnosis of BAH.

**AVS**

AVS has widely been considered the gold standard test for subtype classification in PA. The current clinical practice guidelines advocate use of AVS with measurement of plasma cortisol
concentration (PCC) and plasma aldosterone concentration (PAC). Numerous studies have demonstrated the superiority of AVS over imaging for subtyping of PHA (34-36). Despite these recommendations, the utilization of AVS for subtype classification remains low. In the Adrenal Vein Sampling International Study (AVIS), AVS was systematically performed in only 77% of patients with confirmed PA (37).

Until very recently, the practice that mandated AVS prior to surgical adrenalectomy had gone relatively unchallenged. The SPARTACUS trial (Subtyping Primary Aldosteronism: a Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography scan) examined the outcomes of patients with hyperaldosteronism who underwent treatment based on either CT alone or AVS (38). The primary endpoint of this trial was the intensity of drug treatment to obtain target blood pressure. The secondary endpoints were biochemical outcomes in patients treated with adrenalectomy, health-related quality of life, cost-effectiveness, and safety. After one year follow-up, the trial showed that treatment of PA based on CT or AVS did not show significant difference in intensity of antihypertensive medication or clinical benefits. Additionally, CT and AVS were both found to be safe, but AVS-based approach was significantly more expensive than a CT-based approach for PA. Critics of the study highlight that the study population favored a more florid clinical phenotype of PA that is less likely to achieve blood pressure cure following adrenalectomy (39). How the results of SPARTACUS should be incorporated into the current paradigm of PA remains unsettled.
Normotensive PA

Although hypertension is considered a hallmark of PA, the clinical spectrum of PA may involve normotensive individuals. This nascent form of hyperaldosteronism has recently been characterized. Brown et al performed a longitudinal analysis investigating whether aldosterone concentrations, in the context of physiologic PRA phenotypes were associated with incident hypertension (40). A suppressed renin phenotype was associated with a higher rate of incident hypertension than other PRA phenotypes (incidence rates per 1000 person-years of follow-up: suppressed renin phenotype, 85.4 events [95% CI, 73.4 to 99.3 events]; indeterminate renin phenotype, 53.3 events [CI, 42.8 to 66.4 events]; unsuppressed renin phenotype, 54.5 events [CI, 41.8 to 71.0 events]). With renin suppression, higher aldosterone concentrations were independently associated with an increased risk for incident hypertension, whereas no association between aldosterone and hypertension was seen when renin was not suppressed. Higher aldosterone concentrations were associated with lower serum potassium and higher urinary excretion of potassium, but only when renin was suppressed. These results support a spectrum of subclinical PA that poses significant future risk of incident hypertension. Identifying which patients to screen for this spectrum of PA remains a challenging question.

Successful Adrenalectomy

Once a localizing adrenal lesion is identified, surgical adrenalectomy provides the best opportunity for long-term BP control. Several factors have now been identified that predict the response to surgical adrenalectomy. Wang et al performed a multivariate regression analysis that
examined the major determinants of postoperative cure for PA. The main determinants of surgical cure, included: duration of hypertension less than 5 years, number of antihypertensive medications ≤2, preoperative response to spironolactone, TT genotype of the CYP11B2 gene, and the presence of adenoma rather than hyperplasia. (Table 1) (41). These factors can serve as a powerful tool to aid in the evaluation of patients for adrenalectomy. Additionally, these factors can identify patients who may respond less favorably to adrenalectomy and will need closer post-adrenalectomy monitoring.

Genetics in Sporadic PA

Tremendous advances in our understanding of the genetics responsible for sporadic PA are emerging. The preponderance of insights gained over the last decade suggest that PA is predominantly a genetic disease caused by somatic mutations (42-44). The most frequent genetic variation in APA is a somatic mutation of the KCNJ5 gene, which was first described by Choi et al in 2011 (42). Somatic mutations in the selectivity filter of the KCNJ5 channel in APA result in sodium entry, membrane depolarization, calcium mobilization, resulting in constitutive aldosterone release (43). The prevalence of somatic KCNJ5 mutations in APA is 40-50% worldwide, although a higher prevalence has been reported in populations from China and Japan (45-46).

Identification of the KCNJ5 gene has implications for the clinical and therapeutic management of sporadic PA. A number of studies have investigated the effect of harboring the KCNJ5 gene mutation as it relates to the surgical outcome for PA. In a retrospective study by Almeida et al,
100 patients with PA who were undergoing adrenalectomy were enrolled. The presence of KCNJ5 mutation was the only independent predictor of hypertension remission after adrenalectomy (p=0.004) (47). In a Japanese study, patients harboring APAs with and without KCNJ5 gene mutations were evaluated for arterial stiffness and blood pressure following adrenalectomy (48). The KCNJ5-mutated group displayed a significant improvement in left ventricular mass index (p<0.001), but not in the wild type group (p=0.256). Recent studies have shown the macrolides selectively inhibit mutant KCNJ5 potassium channels and can reduce aldosterone production in individuals with APA (49-50). Although further testing is necessary, these antibiotics may hold promise for the treatment of APAs harboring this mutation. Genetic testing for the KCNJ5 mutation is now commercially available and detailed ordering information can be found at the National Institutes of Health (NIH) Genetic Testing Registry. Currently, however, the clinical utility of KCNJ5 gene mutation identification remains isolated to predicting surgical response to adrenalectomy in APAs and, potentially, in cardiovascular risk stratification.

Innovative Medical Therapy

Several important advances in medical therapy over the last few years may have therapeutic implications for PA in the near future. One such advance is the advent of a novel class of drugs called nonsteroidal mineralocorticoid receptor antagonists (MRAs). Several drugs in this class are under development, including aparanone, finerenone, and esaxerenone. Esaxerenone has recently received marketing approval in Japan for the treatment of hypertension based on positive results of phase III trials (51). Nonsteroidal MRAs tend to have greater receptor selectivity compared to spironolactone, and stronger mineralocorticoid receptor binding affinity
than eplerenone (52). These new class of drugs tend to have improved side effect profiles despite improved potency (53). Additionally, nonsteroidal MRAs have a lower risk of hyperkalemia than traditional MRAs (54). This may afford the opportunity to safely combine ACEi or ARBs with nonsteroidal MRAs for a more complete aldosterone receptor inactivation in PA without subsequent risk of hyperkalemia. These agents will greatly expand the armamentarium of available medical therapy for PA, particularly in BAH and APA patients who are not candidates for surgical adrenalectomy.

Mineralocorticoid receptor activation, atherosclerosis, and inflammation

The blood pressure changes associated with high aldosterone states do not independently explain the tremendous burden of cardiovascular and renal disease within this population (4). Although all the mechanisms responsible for the increased risk of cardiovascular disease and renal disease remain undefined, inflammation and atherosclerosis are two putative factors that have been consistently identified (55,56). Emerging research is elucidating novel mechanisms by which mineralocorticoid receptor (MR) activation initiates a cascade of downstream events that culminate in vascular inflammation and progressive atherosclerosis (Figure 2) (57). MR activation appears to modulate conversion of monocyte/macrophage lineages to a more inflammatory phenotype (58). The beneficial effects of MR blockade on both inflammation and atherosclerosis further implicate MR activation as a causative pathway. The authors, herein, are currently performing a prospective, randomized controlled clinical trial of MR antagonism in type II diabetic patients at high risk of cardiovascular [ClinicalTrials.gov. NCT02169089 (59)]. The purpose of the study is to evaluate the impact of MR antagonism on atherosclerosis progression and monocyte plasticity over time. These important findings and
future research will help clarify important gaps in our knowledge that will ultimately improve the
care of individuals with aldosterone-mediated diseases, including PA. Immune modulation may
be a future therapeutic target to reduce cardiovascular and renal disease in high aldosterone
states.

Conclusion

Nearly seven decades have elapsed since the biochemical and clinical features of PA were
described by Conn. Despite the considerable time lapse, PA remains an underappreciated cause
of both hypertension and target end-organ damage. The failure to recognize PA has a
tremendous, downstream effect on blood pressure control, and, more importantly, incident
cardiovascular diseases. Emerging concepts in the field of PA are rapidly advancing our
understanding of the disease and continually shaping our diagnostic approach. These concepts in
PA will ultimately translate into more curative options being pursued in this high-risk patient
population. This complex and dynamic disease entity warrants a contemporized approach that
incorporates both a historical and a state-of-the-art understanding in order to provide meaningful
clinical outcomes.
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Author Contributions

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Table 1

Variables Associated With Successful Surgical Outcomes for Primary Hyperaldosteronism

| Variables                                         | Adjusted Odds Ratio (95% CI)        | p Value |
|---------------------------------------------------|-------------------------------------|---------|
| Number of antihypertensive agents (<2)             | 2.939 (1.254-5.235)                | p=0.022 |
| Preoperative Response to Spironolactone            | 3.405 (1.681-6.985)                | p=0.006 |
| TT genotype of the CYP11B2 gene                    | 2.765 (1.221-4.986)                | p=0.030 |
| Duration of Hypertension Less than 5 years (months)| 6.515 (2.278-10.293)              | p<0.001 |
| Solitary Adenoma Compared to Nodular Hyperplasia   | 5.274 (2.150-8.141)                | p=0.001 |

Table 1: Multivariate logistic regression revealed that duration of hypertension less than 5 years, number of antihypertensive medication ≤2, preoperative response to spironolactone, TT genotype of CYP11B2, and solitary adenoma (rather than nodular hyperplasia) contributed independently to a predictive model (adapted from “Predictors of successful outcomes after adrenalectomy for primary hyperaldosteronism” Wang W, 2012, *Int Surg.* Page 108.)
References

1. Conn JW: Presidential address. Part I. Painting background. Part II. Primary aldosteronism: a new clinical syndrome. J Lab Clin Med 1955;45:3–17.

2. O'brien, Eoin. “The Lancet Commission on Hypertension: Addressing the Global Burden of Raised Blood Pressure on Current and Future Generations.” The Journal of Clinical Hypertension, vol. 19, no. 6, 2017, pp. 564–568., doi:10.1111/jch.12998.

3. Calhoun, David A., et al. “Hyperaldosteronism Among Black and White Subjects With Resistant Hypertension.” Hypertension, vol. 40, no. 6, 2002, pp. 892–896., doi:10.1161/01.hyp.0000040261.30455.b6.

4. Moniticone S, et al. Cardiovascular events and target end organ damage in primary hyperaldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018;6:41-50.

5. Hundemer GL et al. Cardiometabolic outcomes and mortality in medically treated primary hyperaldosteronism; a retrospective cohort study. Lancet Diabetes Endocrinol. 2018. 6, 51-59.

6. Ohno, Youichi, et al. “Prevalence of Cardiovascular Disease and Its Risk Factors in Primary Aldosteronism.” Hypertension, vol. 71, no. 3, 2018, pp. 530–537., doi:10.1161/hypertensionaha.117.10263.

7. Wu, Jueli, et al. “Assessing the Quality of Guidelines for Primary Aldosteronism.” Journal of Hypertension, vol. 37, no. 7, 2019, pp. 1500–1512., doi:10.1097/hjh.0000000000002046.

8. Rossi, Gian Paolo, et al. “A Prospective Study of the Prevalence of Primary
Aldosteronism in 1,125 Hypertensive Patients.” *Journal of the American College of Cardiology*, vol. 48, no. 11, 2006, pp. 2293–2300., doi:10.1016/j.jacc.2006.07.059.

9. Burrello J, Monticone S, Losano, I et al. “Prevalence of Hypokalemia and Primary Hyperaldosteronism in 5100 Patients Referred to a Tertiary Hypertension Unit.” *Hypertension*, 2020; 75:1025-1033.

10. Brown, J, Siddiqui M, Vaidya A, The Unrecognized Prevalence of Primary Hyperaldosteronism: A cross-sectional study. *Annals of Internal Medicine*. May 2020. 1-12.

11. Milliez, Paul, et al. “Evidence for an Increased Rate of Cardiovascular Events in Patients with Primary Aldosteronism.” *Journal of the American College of Cardiology*, vol. 45, no. 8, 2005, pp. 1243–1248., doi:10.1016/j.jacc.2005.01.015.

12. Monticone, Silvia, et al. “Cardiovascular Events and Target Organ Damage in Primary Aldosteronism Compared with Essential Hypertension: a Systematic Review and Meta-Analysis.” *The Lancet Diabetes &amp; Endocrinology*, vol. 6, no. 1, 2018, pp. 41–50., doi:10.1016/s2213-8587(17)30319-4.

13. Hundemer, Gregory L., et al. “Incidence of Atrial Fibrillation and Mineralocorticoid Receptor Activity in Patients With Medically and Surgically Treated Primary Aldosteronism.” *JAMA Cardiology*, vol. 3, no. 8, 2018, p. 768., doi:10.1001/jamacardio.2018.2003.

14. Rossi, Gian Paolo, et al. “Adrenalectomy Lowers Incident Atrial Fibrillation in Primary Aldosteronism Patients at Long Term.” *Hypertension*, vol. 71, no. 4, 2018, pp. 585–591., doi:10.1161/hypertensionaha.117.10596.

15. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM. Aldosterone excretion among
subjects with resistant hypertension and symptoms of sleep apnea. *Chest.* 2004;125(1):112–117.

16. Di Murro, A. Di, et al. “Renin-Angiotensin-Aldosterone System in Patients with Sleep Apnoea: Prevalence of Primary Aldosteronism.” *Journal of the Renin-Angiotensin-Aldosterone System,* vol. 11, no. 3, 2010, pp. 165–172., doi:10.1177/1470320310366581.

17. Florczak, E, et al. “Clinical Characteristics of Patients with Resistant Hypertension: the RESIST-POL Study.” *Journal of Human Hypertension,* vol. 27, no. 11, 2013, pp. 678–685., doi:10.1038/jhh.2013.32.

18. Shiota, S., et al. “Alterations in Upper Airway Cross-Sectional Area in Response to Lower Body Positive Pressure in Healthy Subjects.” *Thorax,* vol. 62, no. 10, 2007, pp. 868–872., doi:10.1136/thx.2006.071183

19. Dudenbostel T et al. Resistant hypertension, obstructive sleep apnoea, and aldosterone. *J Hum Hypertension.* May; 26(5): 281-7. 2012.

20. Yang L, Zhang H, Effect of spironolactone on patients with resistant hypertension and obstructive sleep apnea. *Clinical and Experimental Hypertension.* Volume 38, Issue 5, 2016.

21. Wolley MJ, Treatment of Primary Hyperaldosteronism is associated with a reduction in the severity of OSA. *J Hum Hypertension.* 855-856 Dec, 31 (12) 2017.

22. Funder, John W., et al. “The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline.” *The Journal of Clinical Endocrinology &amp; Metabolism,* vol. 101, no. 5, 2016, pp. 1889–1916., doi:10.1210/jc.2015-4061.

23. Maiolino, Giuseppe, et al. “Quantitative Value of Aldosterone-Renin Ratio for Detection
of Aldosterone-Producing Adenoma: The Aldosterone-Renin Ratio for Primary Aldosteronism (AQUARR) Study.” *Journal of the American Heart Association*, vol. 6, no. 5, 2017, doi:10.1161/jaha.117.005574.

24. Irony I, Kater CE, Biglieri EG, Shackleton CH. Correctable subsets of primary aldosteronism. Primary adrenal hyperplasia and renin responsive adenoma. Am J Hypertens. 1990;3:576–582

25. Nomura, Kaoru, et al. “Primary Aldosteronism with Normal Aldosterone Levels in Blood and Urine.” *Acta Endocrinologica*, vol. 110, no. 4, 1985, pp. 522–525., doi:10.1530/acta.0.1100522.

26. Increased disorderliness and amplified basal and pulsatile aldosterone secretion in patients with primary aldosteronism. - H Siragy, W Vieweg, S Pincus, J Veldhuis. The Journal of Clinical Endocrinology & Metabolism - 1995

27. Rene Baudrand, Francisco J. Guarda, Jasmine Torrey, Gordon Williams, and Anand Vaidya. Dietary Sodium Restriction Increasing the Risk of Misinterpreting Mild Cases of Primary Hyperaldosteronism. J Clin Endocrinol Metab. 2016 Nov; 101(11): 3989–3996.

28. Tu, Wanzhu, et al. “Age-Related Blood Pressure Sensitivity to Aldosterone in Blacks and Whites.” *Hypertension*, vol. 72, no. 1, 2018, pp. 247–252., doi:10.1161/hypertensionaha.118.11014.

29. DunnickNR, Leight GS Jr, Roubdoux MA, Leder RA, Paulson E, Kurylo L. CT in the diagnosis of primary aldosteronism: sensitivity in 29 patients. AJR Am J Roentgenol1993; 160: 321–324

30. Young, William F., et al. “Role for Adrenal Venous Sampling in Primary
Aldosteronism.” *Surgery*, vol. 136, no. 6, 2004, pp. 1227–1235.,
doi:10.1016/j.surg.2004.06.051.

31. Kempers, Marlies J.e. “Systematic Review: Diagnostic Procedures to Differentiate Unilateral From Bilateral Adrenal Abnormality in Primary Aldosteronism.” *Annals of Internal Medicine*, vol. 151, no. 5, 2009, p. 329, doi:10.7326/0003-4819-151-5-200909010-00007.

32. Williams T, Lenders JW, Mulatero, Burrello J, Rottenkolber M, Adolf C, Satoh F, Amar L, Quinkler M; Primary Aldosteronism Surgery Outcome (PASO) investigators. Outcomes after adrenalectomyOutcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. Lancet Diabetes Endocrinol. 2017 Sep;5(9):689-699. doi: 10.1016/S2213-8587(17)30135-3. Epub 2017 May 30.

33. Lingam, R.k., et al. “Diagnostic Performance of CT versus MR in Detecting Aldosterone-Producing Adenoma in Primary Hyperaldosteronism (Conn’s Syndrome).” *European Radiology*, vol. 14, no. 10, 2004, doi:10.1007/s00330-004-2308-2.

34. Magill, S. B. “Comparison of Adrenal Vein Sampling and Computed Tomography in the Differentiation of Primary Aldosteronism.” *Journal of Clinical Endocrinology & Metabolism*, vol. 86, no. 3, 2001, pp. 1066–1071., doi:10.1210/jc.86.3.1066.

35. Ladurner, Roland, et al. “Accuracy of Adrenal Imaging and Adrenal Venous Sampling in Diagnosing Unilateral Primary Aldosteronism.” *European Journal of Clinical Investigation*, vol. 47, no. 5, 2017, pp. 372–377., doi:10.1111/eci.12746.

36. Schwab CW 2nd, Vingan H, Fabrizio MD. Usefulness of adrenal vein sampling in the evaluation of aldosteronism. *J Endourol*. 2008;22(6):1247-1250.
doi:10.1089/end.2008.000737. Rossi, Gian Paolo, et al. “The Adrenal Vein Sampling International Study (AVIS) for Identifying the Major Subtypes of Primary Aldosteronism.” The Journal of Clinical Endocrinology & Metabolism, vol. 97, no. 5, 2012, pp. 1606–1614., doi:10.1210/jc.2011-2830.

38. Dekkers, Tanja, et al. “Adrenal Vein Sampling versus CT Scan to Determine Treatment in Primary Aldosteronism: an Outcome-Based Randomised Diagnostic Trial.” The Lancet Diabetes & Endocrinology, vol. 4, no. 9, 2016, pp. 739–746., doi:10.1016/s2213-8587(16)30100-0.

39. Rossi, GP Funder J. Adrenal Venous Sampling Versus Computed Tomographic Scan to Determine Treatment in Primary Aldosteronism (The SPARTACUS Trial). A Critique. Hypertension. 2017;69:396–397

40. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, et al. The Spectrum of Subclinical Primary Aldosteronism and Incident Hypertension: A Cohort Study. Ann Intern Med. 2017;167:630–641. [Epub ahead of print 10 October 2017]. doi: https://doi.org/10.7326/M17-0882i:10.1210/jc.2011-2830.

41. Wang Wei et al. Predictors of successful outcomes after adrenalectomy for primary hyperaldosteronism. Int Surg. 97 (2). 104-111. 2012.

42. Choi, M. et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science 331, 768–772 (2011).

43. Boukroun S, Beuschlein F. Prevalence, clinical, and molecular correlates of KCNJ5 mutations in primary hyperaldosteronism. Hypertension. 2012 59:592-8.

44. Nishimoto, K. et al. Aldosterone-stimulating somatic gene mutations are common in normal adrenal glands. Proc. Natl Acad. Sci. USA 112, E4591–E4599 (2015).
44. Wu VC Huang KH, Prevalence and clinical correlates of somatic mutations in aldosterone producing adenoma-Taiwanese population. *Nat Publ Gr.* 2015, 5:1-10

45. Okamura T et al, Characteristics of Japanese aldosterone-producing adenomas with *KCNJ 5* mutations. *Endocrin J.* 2017, 64: 39-47.

46. Scholl, U. I. et al. Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. *Nat. Genet.* 45, 1050–1054 (2013).

47. Vilela LAP, Rassi-Cruz M, Guimaraes AG, et al. *KCNJ5* Somatic Mutation Is a Predictor of Hypertension Remission After Adrenalectomy for Unilateral Primary Aldosteronism. *J Clin Endocrinol Metab.* 2019;104(10):4695-4702. doi:10.1210/jc.2019-00531

48. Chang, Chia-Hui et al. “Arterial stiffness and blood pressure improvement in aldosterone-producing adenoma harboring *KCNJ5* mutations after adrenalectomy.” *Oncotarget* vol. 8,18 (2017): 29984-29995. doi:10.18632/oncotarget.16269

49. Scholl, Ute I et al. “Macrolides selectively inhibit mutant *KCNJ5* potassium channels that cause aldosterone-producing adenoma.” *The Journal of clinical investigation* vol. 127,7 (2017): 2739-2750. doi:10.1172/JCI91733

50. Brasilina Caroccia, Selene Prisco Teresa Maria Seccia Maria Piazza Giuseppe Maiolino and Gian Paolo Rossi *Macrolides Blunt Aldosterone Biosynthesis* A Proof-of-Concept Study in *KCNJ5* Mutated Adenoma Cells Ex Vivo 9 Oct 2017

https://doi.org/10.1161/HYPERTENSIONAHA.117.10226 Hypertension. 2017;70:1238–1242

51. Duggan S. Esaxerenone:First Global Approval. *Drugs.* 2019 Mar;79(4):477-481. doi: 10.1007/s40265-019-01073-5.
52. Barfacker L, Kuhl A, Hillsch A, et al. Discovery of BAY 94-8862: a non-steroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. *ChemMedChem*. 2012; 7(8): 1385-1403.

53. Liu LC, Schutte E, et al. Finerenone: a third generation mineralocorticoid receptor antagonist for the treatment of heart failure and diabetic kidney disease. *Expert Opin Investig Drugs*, 2015, 24 (8): 1123-1135.

54. Flippatos G, Anker SD, et al. A randomized controlled study of finerenone vs eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J*. 2016. 37(27):2105-2114.

55. Gilbert KC, Brown NJ. Aldosterone and Inflammation. *Curr Opin Endocrinol Diabetes Obes*. 2010 Jun;17(3):199-204.

56. de Rita O1, Hackam DG, Spence JD. Effects of aldosterone on human atherosclerosis: plasma aldosterone and progression of carotid plaque. *Can J Cardiol*. 2012 Nov-Dec;28(6):706-11. doi: 10.1016/j.cjca.2012.04.014. Epub 2012 Jun 19.

57. Belden Z.a · Deiuliis J. A.a · Dobre M.b · Rajagopalan S. Inflammation: Focus on Kidney and Vasculature. *Am J Nephrol* 2017;46:298-314 https://doi.org/10.1159/000480652

58. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, Schutz G, et al: Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. *J Clin Invest* 2010;120:3350-336459. Rajagopalan S, Fink J, Weir M. Design of the Magnetic Resonance Imaging Evaluation of Mineralocorticoid Receptor Antagonism in Diabetic Atherosclerosis (MAGMA) Trial. *Clinical Cardiol*. 2017; 40:633-640.
Figure 1

A

24-h Urinary Aldosterone Excretion, µg

Untreated Normotension
Untreated Stage 1 Hypertension
Untreated Stage 2 Hypertension
Treated Resistant Hypertension

Participants, n

B

Probability Density

24-h Urinary Aldosterone Excretion, µg

Untreated normotension
Untreated stage 1 hypertension
Untreated stage 2 hypertension
Treated resistant hypertension

C

24-h Urinary Aldosterone Excretion, µg

Untreated normotension
Unadjusted
Adjusted

Untreated stage 1 hypertension
Unadjusted
Adjusted

Untreated stage 2 hypertension
Unadjusted
Adjusted

Treated resistant hypertension
Unadjusted
Adjusted
Figure 1: The distribution of renin-independent aldosterone production by blood pressure category. A. Unadjusted urinary aldosterone excretion rate (y-axis) for each individual participant, ordered from lowest to highest (x-axis). The dashed line represents the 12 ug/24 hour threshold for the diagnosis of PA. B. Unadjusted density plots for renin-independent aldosterone production, by blood pressure category. C. Mean urinary aldosterone excretion rates for each blood pressure category, unadjusted (solid lines with circles) and adjusted (dotted lines with squares). Adapted with permission from Brown et al (10).
Figure 2: The Adverse Consequences of Mineralocorticoid Receptor Activation. Adapted illustration by Philip Wilson.