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

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## 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 because 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 effect these advances have on both diagnostic and therapeutic modalities.**


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## 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 BP globally (2). Among the key steps proposed to combat elevated BP was better identification of individuals with secondary hypertension. The hope is that a more streamlined evaluation for secondary hypertension would equate to better identification, treatment, and potential cures for individuals with secondary forms of hypertension.

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 with individuals with essential hypertension (EH) (4–6). Compared with individuals with EH, the presence of hyperaldosteronism increased the risk of myocardial infarction, stroke, and atrial fibrillation (AF) on the magnitude of fourfold, sixfold, 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 of 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 workup 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 Primary Aldosteronism Prevalence in Hypertension (PAPY) 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 aldosterone-producing adenomas (APA) had concomitant spontaneous hypokalemia. The presence of hypokalemia does suggest a more florid clinical phenotype of 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 with bilateral adrenal hyperplasia (BAH) (49% versus 16%). The patients with hypokalemia and APA tended to have higher aldosterone/renin ratio (ARR) values, which generally favor a more complete clinical response to surgical adrenalectomy. Taken together, these findings provide compelling data that hypokalemia is not

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a consistent hallmark of PA, but is, rather, a crude tool to differentiate APA from BAH and to predict response to surgical adrenalectomy in APA.

A more recent study showed contradictory observations regarding the prevalence of hypokalemia in PA compared with early observations. Burrello *et al.* (9) 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. Among patients with spontaneous hypokalemia, the prevalence of PA increased from 22% in patients with potassium of 3.5–3.6 mmol/L up to 89% 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. Because 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.* (9), the prevalence of cardiovascular events was higher in patients with hypokalemia compared with normokalemia (11% versus 6%, $P<0.001$). Specifically, patients with hypokalemia displayed a higher risk of arrhythmias (3% versus 2%, $P=0.006$), heart failure (1% versus 0.4%, $P=0.032$), and stroke (3% versus 1%, $P<0.001$). Lastly, patients with hypokalemia demonstrated a higher prevalence of CKD (9% versus 3%, $P<0.001$). Future studies are necessary to further elucidate the association between

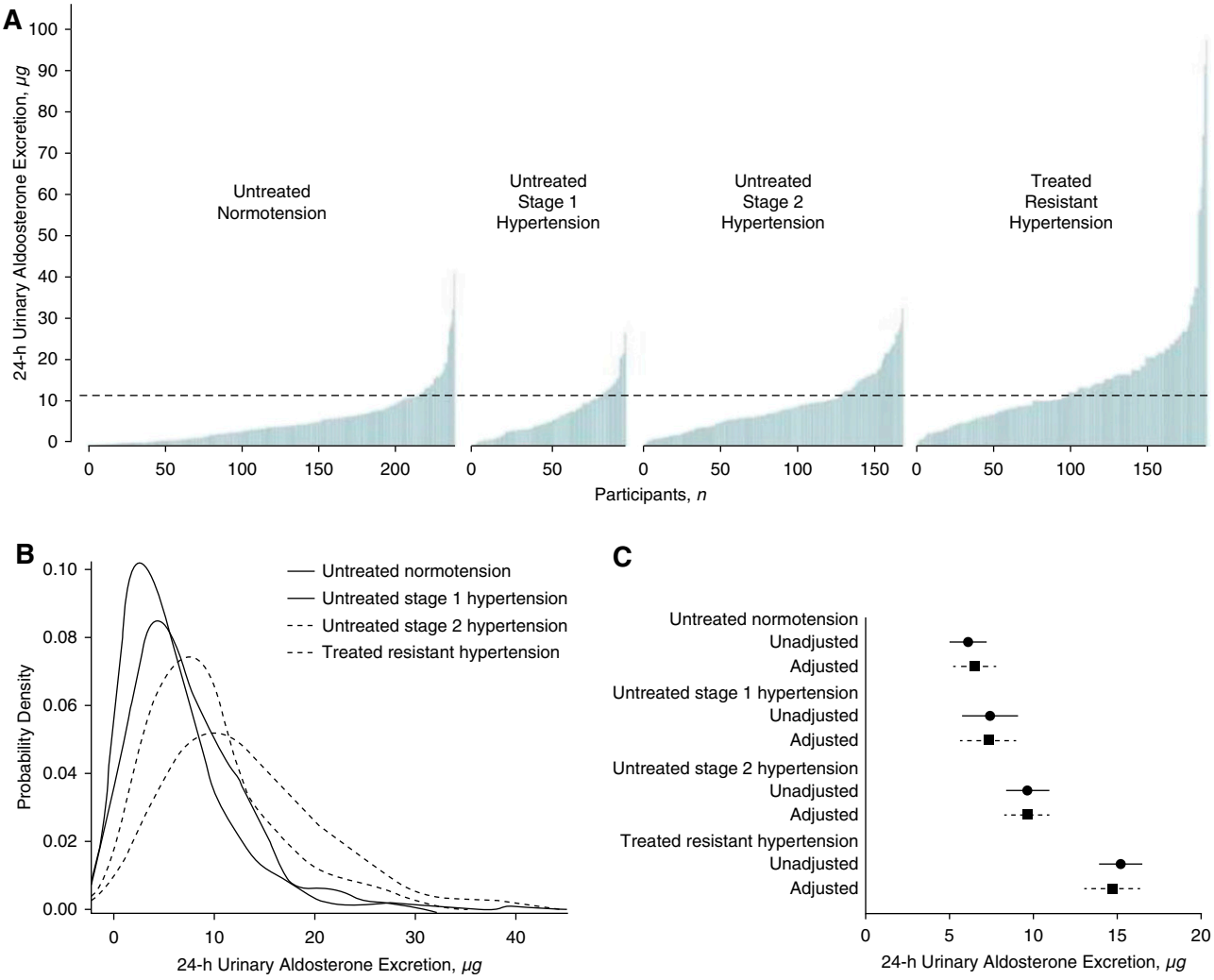


**Figure 1.** | **The distribution of renin-independent aldosterone production by BP category.** (A) Unadjusted urinary aldosterone excretion rate (*y* axis) for each individual participant, ordered from lowest to highest (*x* axis). The dashed line represents the 12 μg/24 hr threshold for the diagnosis of primary hyperaldosteronism. (B) Unadjusted density plots for renin-independent aldosterone production, by BP category. (C) Mean urinary aldosterone excretion rates for each BP category, unadjusted (solid lines with circles) and adjusted (dotted lines with squares). Modified from reference 10, with permission.

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 into 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 >1000 patients from four geographically diverse centers in the United States. 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 individuals who are normotensive and normokalemic), 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 because, even among individuals with normotension, 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 AF and obstructive sleep apnea (OSA). A strong association between PA and AF has been observed in the past decade. Milliez *et al.* (11) recently examined the rate of cardiovascular events in patients with PA and observed a 12-fold increased risk of AF in PA compared with EH (PA, 7.3; EH, 0.6; odds ratio, 12.1; $P<0.001$). These results were confirmed by Monticone *et al.* (4), who performed a systematic review and meta-analysis of 31 studies to examine the rates of cardiovascular events among participants with PA compared with EH. The risk of AF was 3.52 (95% CI, 2.06 to 5.99) in the participants with PA compared with EH.

Interestingly, the completeness of aldosterone blockade in PA may affect the future risk of developing AF. Hundemer *et al.* (12) investigated whether mineralocorticoid receptor (MR) antagonist (MRA) therapy or adrenalectomy in PA influence the risk for incident AF. Patients with PA who were treated with surgical adrenalectomy had no statistically significant difference in risk for incident AF compared with EH. Despite similar BP control, patients with PA treated with MRAs had a higher risk for incident AF, compared with EH, when the renin levels remained suppressed on MR blockade. Conversely, patients with PA who were treated with MRAs and experienced an increase in renin or had surgical adrenalectomy had no statistically significant difference in risk for incident AF compared with patients with EH. Similarly, Rossi *et al.* (13) recently published results showing that adrenalectomy significantly lowered incident AF in patients with PA. After a median follow-up of 11.8 years, medically treated PA showed a lower AF-free survival than patients with PA who were 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.* (14). Subjects at high risk of OSA were almost two times more likely to have PA (36% versus 19%). The frequency of PA in patients with OSA was evaluated in the study of Di Murro *et al.* (15). The authors included 325 consecutive patients with newly diagnosed hypertension. Of the patients with OSA, 34% were also diagnosed with PA, and BAH was identified as the most common subtype of PA. In the Resist-POL study, 204 consecutive patients with resistant hypertension were evaluated (16). OSA was marginally, but significantly, higher in individuals with PA than in those without PA. Moderate-to-severe OSA tended to occur more frequently in patients with PA compared with 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 (17). 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 (18). Moreover, therapies directed at aldosterone excess in OSA and resistant hypertension appear to have profound clinical benefits. For instance, Yang *et al.* (19) examined the effects of spironolactone on patients with resistant hypertension (not confirmed to have PA) and OSA. After 12 weeks of follow-up, the apnea-hypopnea index (21.8–1.8, $P<0.05$), plasma aldosterone levels ng/dl (9.8–2.9, $P<0.05$), clinic BP, and ambulatory BP were reduced significantly in the treatment group compared with the control group. Similar results have been identified in patients with PA. Wolley *et al.* (20) 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 BAH were treated with surgical adrenalectomy and MR 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 ($P=0.02$) (20). 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 before subtype classification (21). Confirmatory testing for PA can be performed through oral sodium loading, saline infusion test, fludrocortisone

suppression test, or captopril challenge test. 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 (22). 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 captopril challenge test 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 and the positive likelihood ratio were high (6.35 and 17.7, respectively) for ARR values >50. Taken together, these results imply that ARR is a highly effective screening test for PA and, even more surprisingly, an ARR value >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) >20 ng/dl (21). Because 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, broadscale application of confirmatory testing in the evaluation of PA appears misguided (22–24).

## Normal Aldosterone PA

PA can occur in the setting of relatively normal PAC (20). There are a few plausible explanations for this paradoxic phenomenon. Aldosterone is secreted in a pulsative manner that generally occurs more readily in the early morning (25). 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 (26). PAC levels can be normal despite a clinical phenotype of PA due to variation in aldosterone sensitivity. Age and race appear to be major determinants of sensitivity to aldosterone. Tu *et al.* (27) found that the effect of aldosterone on BP intensified as age increased, especially in black individuals ($P<0.01$), suggesting an increased aldosterone sensitivity with age. In comparison to black people, age-related changes in aldosterone sensitivity in white individuals were not statistically significant. These findings raise concern about using the absolute value of PAC as an inclusion criterion 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 with adrenal vein sampling (AVS) because 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 (28). 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 PA were selected prospectively for AVS on the basis of degree of aldosterone excess, age, desire for surgical treatment, and CT findings (29). On the basis of CT findings alone, nearly 22% of patients would have been inappropriately excluded from adrenalectomy. Furthermore, nearly 25% of the patients might have undergone unnecessary or inappropriate adrenalectomy. In a systematic review, Kempers *et al.* (30) found that CT/MRI results did not agree with AVS results in 38% of patients. More specifically, if only CT/MRI results had been used to determine lateralization of an adrenal abnormality, inappropriate adrenalectomy would have occurred in 15% of patients (where AVS showed a bilateral problem), inappropriate exclusion from adrenalectomy would have occurred in 19% (where AVS showed unilateral secretion), and adrenalectomy on the wrong side would have occurred in 4% (where AVS showed aldosterone secretion on the contralateral side). In a more current study from Munich, in 175 patients who underwent unilateral laparoscopic adrenalectomy for PA after CT/MRI and lateralization by AVS, CT imaging and MRI showed discordant results of 39% and 41%, respectively (31). 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 BAH rather than discrete adrenal adenomas. Lingam *et al.* (32) found that the adrenal glands in patients with BAH were significantly ($P<0.05$) larger than those in patients with APA or in healthy control subjects. A sensitivity of 100% was achieved when a mean limb width of >3 mm was used to diagnose BAH, and a specificity of 100% was achieved when the mean limb width was ≥5 mm. In the future, broad application of limb width measurement of the adrenal glands may be a 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 and PAC. Numerous studies have demonstrated the superiority of AVS over imaging for subtyping of PHA (33–35). Despite these recommendations, the use 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 (36).

Until very recently, the practice that mandated AVS before surgical adrenalectomy had gone relatively unchallenged.

The SPARTACUS (Subtyping Primary Aldosteronism: a Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography scan) trial examined the outcomes of patients with hyperaldosteronism who underwent treatment based on either CT alone or AVS (37). The primary end point of this trial was the intensity of drug treatment to obtain target BP. The secondary end points were biochemical outcomes in patients treated with adrenalectomy, health-related quality of life, cost effectiveness, and safety. After 1 year follow-up, the trial showed that treatment of PA based on CT or AVS did not show significant differences in intensity of antihypertensive medication or clinical benefits. Additionally, CT and AVS were both found to be safe, but an 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 BP cure after adrenalectomy (38). 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 individuals who are normotensive. This nascent form of hyperaldosteronism has recently been characterized. Brown *et al.* (39) performed a longitudinal analysis investigating whether aldosterone concentrations, in the context of physiologic plasma renin activity phenotypes, were associated with incident hypertension. A suppressed renin phenotype was associated with a higher rate of incident hypertension than other plasma renin activity 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 [95% CI, 42.8 to 66.4 events]; unsuppressed renin phenotype, 54.5 events [95% 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.* (40) 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 <5 years, number of antihypertensive medications less than or equal to two, preoperative response to spironolactone, TT genotype of the CYP11B2 gene, and the presence of adenoma rather than hyperplasia. (Table 1) (40).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 postadrenalectomy 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 (41–43). The most frequent genetic variation in APA is a somatic mutation of the *KCNJ5* gene, which was first described by Choi *et al.* (41). Somatic mutations in the selectivity filter of the *KCNJ5* channel in APA result in sodium entry (44), membrane depolarization, and calcium mobilization, resulting in constitutive aldosterone release (42). 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 because it relates to the surgical outcome for PA. In a retrospective study by Almeida and-colleagues (47), 100 patients with PA who were undergoing adrenalectomy were enrolled. The presence of the *KCNJ5* mutation was the only independent predictor of

**Table 1. Variables associated with successful surgical outcomes for primary hyperaldosteronism**

| Variables | Adjusted Odds Ratio (95% CI) | *P* Value |
|---|---|---|
| Number of antihypertensive agents (≤2) | 2.94 (1.25 to 5.24) | 0.02 |
| Preoperative response to spironolactone | 3.41 (1.68 to 6.99) | 0.006 |
| TT genotype of the CYP11B2 gene | 2.77 (1.22 to 4.99) | 0.03 |
| Duration of hypertension <5 yr (mo) | 6.52 (2.28 to 10.29) | <0.001 |
| Solitary adenoma compared to nodular hyperplasia | 5.27 (2.15 to 8.14) | 0.001 |

Multivariate logistic regression revealed that duration of hypertension <5 yr, 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. Modified from reference 40, with permission.

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 BP after 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 ($P=0.26$). 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 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 MRAs. Several drugs in this class are under development, including apararenone, finerenone, and esaxerenone. Esaxerernone has recently received marketing approval in Japan for the treatment of hypertension based on positive results of phase 3 trials (51). Nonsteroidal MRAs tend to have greater receptor selectivity compared with spironolactone, and stronger MR binding affinity than eplerenone (52). These new classes 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 angiotensin-converting enzyme inhibitors or angiotensin receptor blockers 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 patients with BAH and APA who are not candidates for surgical adrenalectomy.

## MR Activation, Atherosclerosis, and Inflammation

The BP changes associated with high aldosterone states do not independently explain the tremendous burden of cardiovascular and renal disease within this population (4). Although all of 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 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 patients with type 2 diabetes who are at high risk of cardiovascular (ClinicalTrials.gov identifier, NCT02169089) (59). The purpose of the study is to evaluate the effect 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

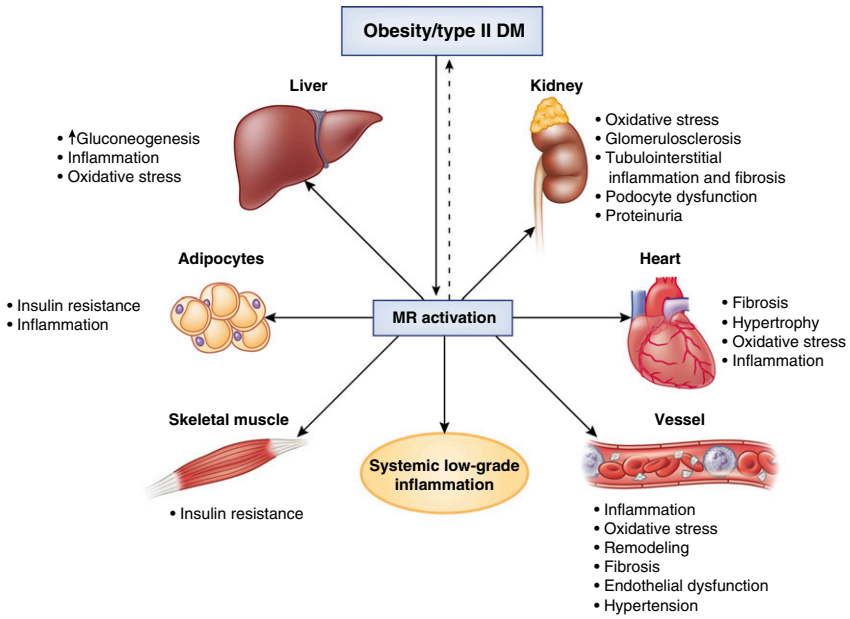


**Figure 2.** | **The adverse consequences of mineralocorticoid receptor activation.** DM, diabetes mellitus; MR, mineralocorticoid receptor.

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 BP 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 to provide meaningful clinical outcomes.

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### Author Contributions

M. Lattanzio was responsible for data curation and investigation; M. Lattanzio and M. Weir conceptualized the study, were responsible for resources, wrote the original draft, and reviewed and edited the manuscript; and M. Weir was responsible for supervision, validation, and visualization.

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