HYPERALDOSTERONISM

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ABSTRACT

Aldosterone regulation plays a crucial role in maintaining intravascular and effective circulating volume and potassium homeostasis; however, inappropriate regulation of aldosterone results in adverse cardiovascular and metabolic consequences. Hyperaldosteronism can be seen in a broad range of phenotypes. Approaching hyperaldosteronism by assessing plasma renin activity and hypertensive status is a simple method to narrow the potential etiologies. Breakthroughs in genetic and histopathological research have resulted in a major paradigm shift in understanding the causes of primary aldosteronism (PA). Germline and somatic mutations in membrane channels, such as potassium channels, that maintain the resting potential of zona glomerulosa cells have been implicated in a large subset of aldosterone producing adenomas. Approaching the diagnosis of PA with an initial screening test is recommended; an aldosterone/renin ratio (ARR)>20-30 ng/dl per ng/(ml·h) when the PRA is suppressed is highly suggestive of PA. Confirmation of autonomous aldosterone excess using recommended suppression tests should prompt imaging studies to localize the source of aldosterone excess. Adrenal venous sampling can be considered in most cases to confirm the location as unilateral or bilateral, and prevent erroneous diagnoses and treatment plans; however, some emerging data suggest that the use AVS may not influence outcomes as much as previously considered. In cases of unilateral PA, surgical treatment typically results in cure of hyperaldosteronism, and substantial improvements in blood pressure and potassium homeostasis. In cases of bilateral disease, and in unilateral disease where surgery is not preferred, medical management with mineralocorticoid receptor antagonists is usually effective.

INTRODUCTION

Aldosterone is the principal mineralocorticoid in man. Its classical functions include regulation of extracellular volume and electrolyte homeostasis through its effects on the renal distal convoluted tubule. In this manner, aldosterone activates the mineralocorticoid receptor in principle cells of the distal nephron, resulting in increased expression of luminal epithelial sodium channels (ENaC) (1). Sodium is reabsorbed via ENaC resulting in a potent

electronegative luminal potential that induces the efflux of cations from the principle cell, namely potassium and hydrogen ions. Thus, the net effect of this classical aldosterone action on the kidney is reabsorption of sodium (which ultimately will result in water reabsorption and intravascular volume expansion) and urinary excretion of potassium and hydrogen.

In addition to these classical actions of aldosterone in the kidney, the non-classical extra-renal actions of aldosterone, particularly on cardiovascular tissues such as the endothelium and myocardium, are now increasingly recognized in human disease (2,3).

ALDOSTERONE REGULATION AND ACTION

Physiologic Actions of Aldosterone

Aldosterone is synthesized in the zona glomerulosa of the adrenal gland. Its production is restricted to this layer of the adrenal cortex because of zonal-specific expression of aldosterone synthase (CYP11B2)(4), which is the key enzyme for aldosterone biosynthesis (5). Its expression is controlled by aldosterone secretagogues. Previous Immunohistochemistry studies of the adrenal gland reported that in early ages, cells express CYP11B2 in a continuous mode, whereas with increasing age, expression of CYP11B2 is less continuous, and thus in adults, CYP11B2-expressing cells are distributed in a diffuse manner in the subcapsular cortex among typical *zona glomerulosa* cells not expressing the enzyme; the CYP11B2-expressing area decreases with age (5,6). Aldosterone secretion is under the control of several factors: angiotensin II, potassium, and, to a lesser degree, adrenocorticotropic hormone (ACTH), endothelin 1 (ET-1), estrogens, and urotensin II (5,7). Its production can be upregulated acutely following increased expression and phosphorylation of the StAR protein or more chronically due to increased expression of CYP11B2 (5).

The renin-angiotensin system (RAS) is a principal regulator of aldosterone production. Renin, an enzyme produced in the juxtaglomerular apparatus of the kidney, catalyses the conversion of angiotensinogen (an inactive precursor peptide) to angiotensin I. Angiotensin I undergoes further enzymatic conversion by angiotensin-converting enzyme (ACE) to produce angiotensin II (AngII). AngII acts via the adrenal angiotensin receptor to stimulate the release of aldosterone by increasing the transcription of aldosterone synthase.

The physiologic role of the RAS is to regulate sodium homeostasis and thereby intravascular volume and arterial pressure. In normal physiology, renin secretion is stimulated by decreased delivery of chloride ion to the macula densa of the juxtaglomerular apparatus. This is typically the consequence of decreased systemic arterial pressure resulting in decreased renovascular pressure and glomerular filtration. Increased renin activity results in activation of the RAS and increased synthesis of AngII, an activator of Ca^{2+} influx and Ca^{2+}/calmodulin-dependent protein kinases (CaMKs), stimulating transcription of CYP11B2 and aldosterone biosynthesis (5). AngII has many functions to counter the initial hypotensive and hypoperfusion insult:

- AngII acts as a direct arterial vasopressor and can induce vasoconstriction to address the systemic hypotension
- AngII stimulates vasopressin (antidiuretic hormone) release to induce distal nephron water reabsorption and expand intravascular volume
- AngII acts at the proximal tubule of the nephron to maximize proximal sodium (and therefore water) reabsorption to expand intravascular volume

- AngII maximizes renal sodium reabsorption by stimulating adrenal aldosterone synthesis; aldosterone then acts at the principle cell to increase sodium reabsorption as described earlier.

The net effect of these actions is a feedback loop whereby expansion of intravascular volume increases renal perfusion and glomerular filtration and decreases renin secretion (Figure 1).

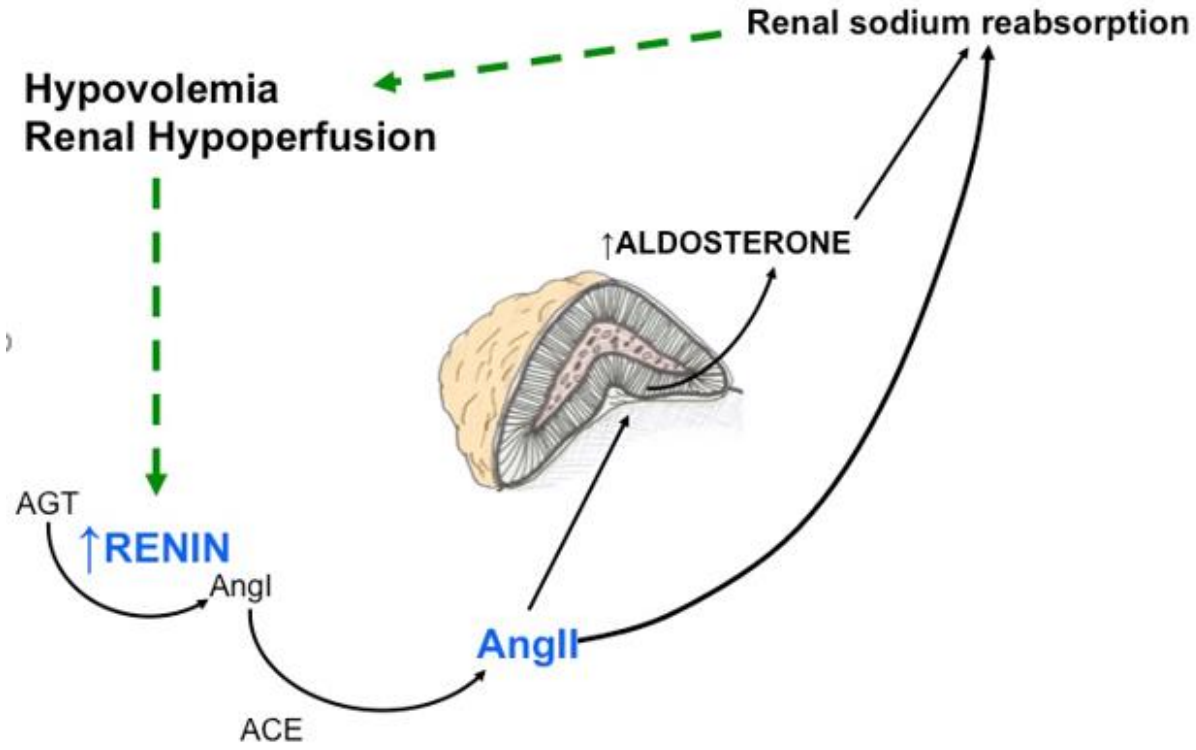

Figure 1. Renin-Dependent Aldosteronism. The physiologic relationship between the renin-angiotensin system and aldosterone regulation is referred to as "Renin-Dependent Aldosteronism," also referred to as "Secondary Aldosteronism." Decreased renal-vascular perfusion resulting in decreased glomerular filtration is sensed by juxtaglomerular cells. The consequent release of renin activates the renin-angiotensin system resulting in the synthesis of angiotensin II (AngII). AngII induces systemic vasoconstriction, increases proximal tubular sodium reabsorption, and stimulates aldosterone secretion. The net effect is increased renal sodium reabsorption and intravascular volume expansion which closes the feedback loop and corrects the initial stimulus to raise renin.

Aldosterone secretion can also be directly stimulated by high serum potassium, which increases transcription of aldosterone synthase in the zona glomerulosa. Potassium channels TASK-1, TASK-2, and TASK-3, coded by KCNK3, KCNK5, and KCNK9 genes, the TWIK-related potassium channel 1, and the G protein-activated inwardly rectifying potassium channel Kir3.4, which is coded by KCNJ5 and transports potassium out of the cell, keeping adrenocortical cells hyperpolarized under resting conditions (5,8).

ACTH is another aldosterone secretagogue, although its effect is modest and transient; ACTH is a 39-amino acid peptide, resulting from the cleavage of its proopiomelanocortin (POMC) precursor. It is produced by the anterior pituitary corticotropes, but, to a lesser degree, can be produced in the brain, adrenal medulla, skin, and placenta (9). It binds to melanocortin type 2 receptor (MC2R), stimulating both cortisol and aldosterone secretion (9). However, earlier and more recent data have suggested that the ACTH effect on aldosterone secretion may be more complex and underestimated. It has been reported that increasing StAR expression, as well as activation of the PKA pathway and calcium/calmodulin-dependent protein kinase, may lead to increased aldosterone secretion (10). A recent study evaluated 61 normotensive and 113 hypertensive patients with normal aldosterone suppression in a combined fludrocortisone-dexamethasone suppression test (dexamethasone was administered to eliminate any stimulatory effect of ACTH on aldosterone secretion) and normal findings in computed tomography. All the patients underwent stimulation tests with 0.03 μg ACTH and among them, twenty-six individuals also had genetic studies. The study found that 27% of the hypertensive group exhibited increased aldosterone secretion following the test. Sequencing of the *KCNJ5* gene revealed that 2 patients had two different heterozygous germline mutations. Interestingly, MR antagonist therapy was effective for blood pressure normalization (11). These findings led to the hypothesis that glomerulosa cells were primed by chronic stress-induced ACTH secretion, and, hence, became more sensitive to ACTH and/or REN/angiotensin II (11,12).

Pathophysiologic Actions of Aldosterone

Emerging evidence has implicated aldosterone, and specifically activation of the mineralocorticoid receptor, with cardiovascular and cardiometabolic diseases (13,14). The mineralocorticoid receptor is classically considered in the context of its expression in the distal nephron; however, it is now clear that this receptor is also expressed in the vasculature and heart and plays an important role in mediating cardiovascular pathophysiology. The non-classical effects of aldosterone have stemmed from dysregulated aldosterone physiology being linked with deleterious end-organ effects. Typically, this has been evidenced by inappropriately elevated levels of aldosterone in the setting of high dietary sodium intake (subclinical or clinical primary hyperaldosteronism). However, some evidence also suggests that inappropriately low levels of aldosterone on a restricted sodium diet, or in response to angiotensin II, are also associated with adverse cardiometabolic consequences (15–17).

Excess or inappropriate aldosterone activity has been associated with or shown to cause cardiac fibrosis, inflammation, and remodelling (18–20), pathologic insulin secretion and/or peripheral resistance, as well as the metabolic syndrome (17,21,22), kidney injury (23), and increased mortality (24). Intervention studies in animals and humans have supported these assertions by demonstrating the prevention of these deleterious effects with the use of mineralocorticoid antagonists (24,25). Taken together, this evolving body of evidence points towards subclinical aldosterone excess, particularly in the milieu of excessive dietary sodium intake, as a modifiable cardio-metabolic risk factor.

The mechanisms by which this can occur are many: 1) an adrenal tumor that autonomously secretes aldosterone; 2) unilateral or bilateral hyperplasia of the zona glomerulosa that oversecretes aldosterone; 3) or germline or somatic mutations that induce aldosterone hypersecretion that is decoupled from AngII signalling. Autonomous aldosterone excess results in continuous renal sodium reabsorption, intravascular volume expansion, hypertension, and renal-vascular hyperperfusion, and consequently

suppression of the RAS. Yet despite this physiologic suppression of the RAS, aldosterone secretion continues unabated, resulting in a vicious cycle of hypertension and possibly also hypokalemia (Figure 2). Patients with PA, when compared with matched essential hypertensives, have increased left ventricular wall and carotid intima media thickness, as well as impaired diastolic and endothelial function (14,26,27). A higher incidence of atrial fibrillation, often hypokalemia-induced, coronary artery disease, and heart failure has been reported (28,29). PA is also associated with a higher incidence of negative cardiovascular outcomes (myocardial infarction and stroke) than essential hypertension with similar degree of blood pressure elevation (30–32). Therefore, PA is considered to induce increased cardiovascular risk independent of blood pressure effects alone. The excess cardiovascular events associated with hyperaldosteronism were previously considered reversible if treatment with mineralocorticoid antagonists was administered in time (33,34). However, newer data suggest that PA patients treated with MR antagonists had an approximately two-fold higher incidence of adverse cardiovascular events. Patients with PA also had a significantly higher death risk, as well as a higher incidence of atrial fibrillation and diabetes mellitus than people diagnosed with essential hypertension. The adjusted 10-year cumulative incidence difference for occurrence of cardiovascular morbidity for patients with PA and treatment with MR antagonists was reported to be 14.1 (95% CI 10.1-18.0) excess events per 100 individuals compared to those with essential hypertension (28).

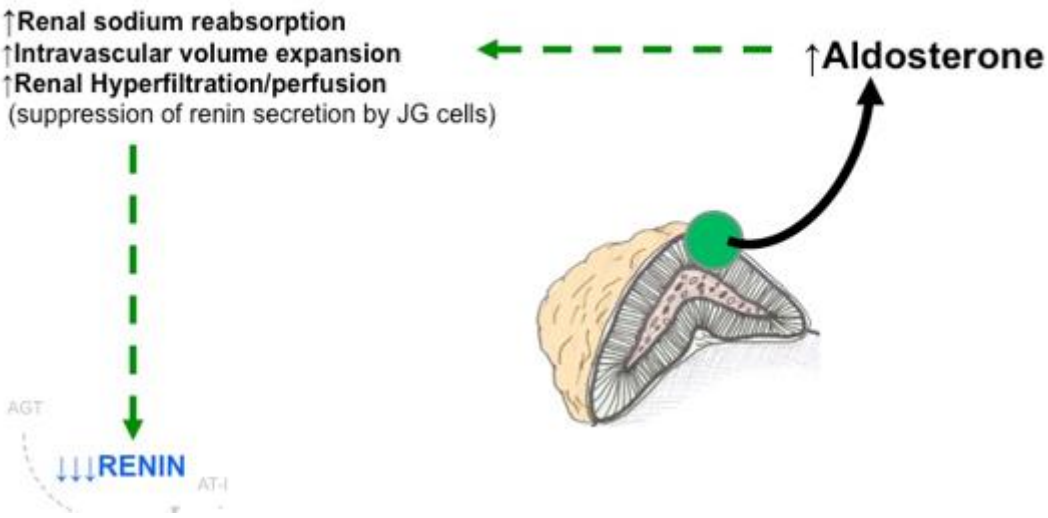

Figure 2: Renin-Independent Aldosteronism or Primary Aldosteronism. The pathophysiologic relationship between the renin-angiotensin system and aldosterone regulation in Primary Aldosteronism is referred to as "Renin-Independent Aldosteronism". See concept video at: https://www.youtube.com/watch?v=db9v9kNIiXU.

CAUSES OF MINERALOCORTICOID EXCESS SYNDROME

Mineralocorticoid excess states (Figure 3) comprise a group of disorders that can be separated into those mediated by the principal mineralocorticoid,

aldosterone, and those caused by non-aldosterone etiologies (35).

Hyperaldosteronism can result from autonomous secretion of aldosterone from one or both adrenal glands, which is referred as PA. In this circumstance, the plasma renin activity (PRA) is suppressed (*hyporeninemic hyperaldosteronism or renin-independent aldosteronism*), and the plasma aldosterone to renin activity ratio is elevated. In secondary hyperaldosteronism, increased activation of the RAS is the initiating event, resulting in excess aldosterone production (*hyperreninemic hyperaldosteronism or renin-dependent aldosteronism*). Therefore, secondary hyperaldosteronism can be a normal physiologic phenomenon (such as in states of systemic hypovolemia or hypoperfusion) or can manifest as a pathologic entity when activation of the RAS is inappropriate relative to the state of the systemic vasculature. The distinction between primary and secondary causes of hyperaldosteronism is of importance, as the manifestations, as well as the subsequent testing and treatment, differ (35).

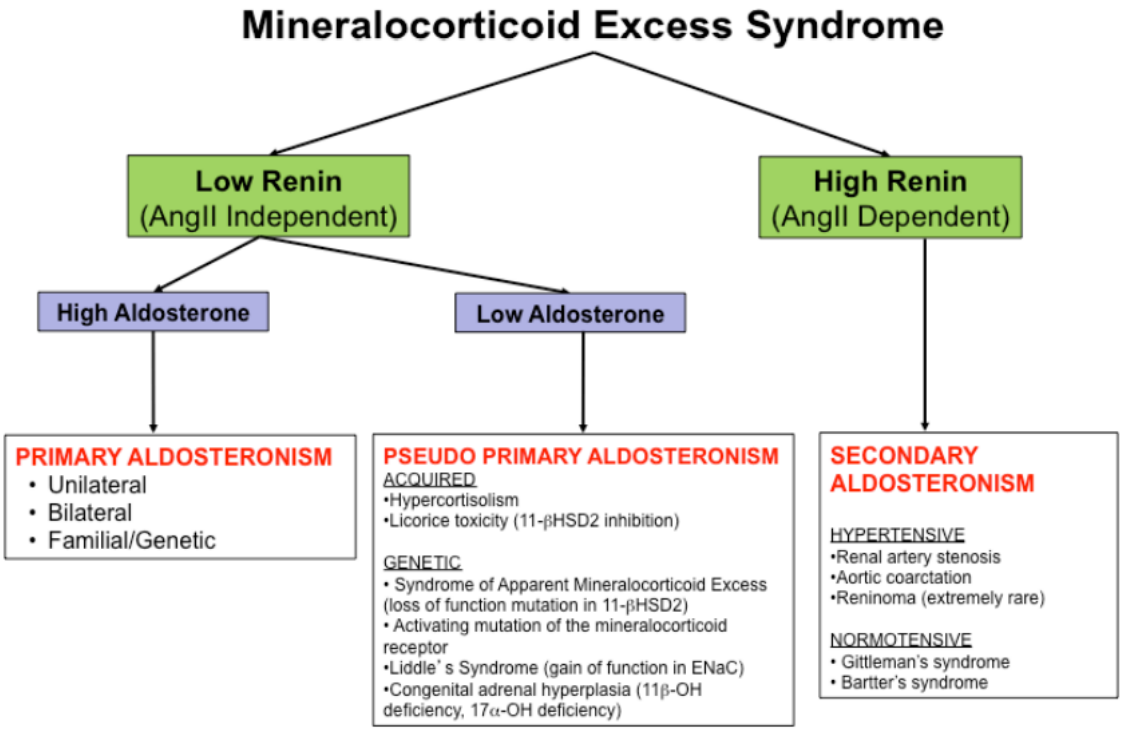

Figure 3. The Approach to Mineralocorticoid Excess Syndromes. See concept video at https://www.youtube.com/watch?v=db9v9kNIiXU. Evaluation of renin as suppressed or unsuppressed is often the first algorithmic step to determine whether the underlying pathophysiology is renin or AngII-dependent versus renin or AngII-independent. Renin-independent states (low renin) can be further characterized as having a relatively high aldosterone (primary aldosteronism) or a suppressed aldosterone (pseudo primary aldosteronism). High renin states represent secondary aldosteronism and may present with hypertension or normotension, depending on the nature of disease.

CAUSES OF MINERALOCORTICOID EXCESS WITH LOW PLASMA RENIN ACTIVITY

Primary Aldosteronism

The five established morphological subtypes of PA include: aldosterone-producing adenoma (APA), bilateral adrenal hyperplasia (BAH), unilateral adrenal hyperplasia (UAH), glucocorticoid-remediable aldosteronism (GRA), and, rarely, adrenocortical carcinoma. A potential sixth subtype may involve a morphologically normal adrenal gland (without any tumor or hyperplasia) that harbors clusters of increased expression of aldosterone synthase: the aldosterone producing cell cluster (36,37). Recent advances in genetics and clinical research have dramatically enhanced our understanding of the pathogenesis of these subtypes and have raised the question of whether these entities are part of a larger spectrum of disorders that share genetic underpinnings (5,6).

APA/BAH/UAH

It is currently estimated that APA or UAH account for 30-40% of PA cases, whereas BAH accounts for the remaining 60% (38–40). Definitive diagnosis of the cause of PA can be a challenge in individual patients; however, making the correct diagnosis is of utmost importance, since the treatment for each underlying etiology may be different. APAs are often small tumors, usually less than 2 cm in diameter. Histopathology of APA reveals hybrid cells which have histological features of both zona glomerulosa and zona fasciculata cells. Unilateral adrenal hyperplasia (UAH), sometimes referred to as primary adrenal hyperplasia, shares many biochemical features with APA. This diagnosis is often made based on evidence of unilateral production of aldosterone in the absence of a discrete radiographic mass. Similar to APA, the hypertension and biochemical abnormalities with UAH may be cured or substantially ameliorated with unilateral adrenalectomy (40,41). BAH probably represents a spectrum of disorders (42,43). The extent of hyperaldosteronism is often milder in BAH compared to APA, and consequently the severity of hypertension, hypokalemia and suppression of PRA is often less. Adrenal carcinomas are a rare cause of primary aldosteronism. At the time of diagnosis, adrenal carcinomas are generally large (>4 cm) and may be producing one or multiple adrenal cortical hormones, including cortisol, aldosterone, and adrenal androgens.

EPIDEMIOLOGY OF ALDOSTERONE EXCESS

Epidemiology of Primary Aldosteronism

In 1954, Conn first reported the clinical syndrome of hypertension, hypokalemia, and metabolic alkalosis resulting from autonomous production of aldosterone due to an adrenal adenoma – a syndrome that continues to bear his name. Previous studies reported a prevalence of primary aldosteronism (PA) of 1-2 %, even in patients with adrenal incidentaloma and hypertension (44). Since that time, numerous studies have investigated the prevalence of primary aldosteronism (PA) and reported rates ranging up to 20%, pending on the cut-offs of screening and diagnostic tests used (45–49). Disparity in these percentages is probably due to the use of different laboratory screening techniques, different definitions of a positive screening study indicative of PA, study design, and varying population ethnicity, and sampling source (21,42,43,50–52). Initial studies

primarily diagnosed patients with PA if they had both hypertension and spontaneous (not diuretic-induced) hypokalemia. More recent reports, however, describe hypokalemic PA in only the minority of PA cases (<40%) (53), and describe an intermediate phenotype of normotensive PA with milder manifestations than the classic hypertensive PA (45,47,50–52,54–56). Many (up to 63%) of patients with PA may be normokalemic (30,44). A recent study suggested that PA was diagnosed in 12% of normotensive and normokalemic people with adrenal incidentalomas (12,56).

In patients with resistant hypertension, the addition of a mineralocorticoid antagonist has been associated with substantial efficacy in blood pressure lowering, suggesting that subclinical hyperaldosteronism may be more prevalent than recognized, within a range 17 and 23 % (44,57,58). In a study involving 1616 patients with resistant hypertension, 21% (338 pts) had an ARR of > 65 with concomitant plasma aldosterone concentrations of > 416 pmol/L (15 ng) (59). After salt suppression testing, only 11% (182 pts) of these patients had primary aldosteronism (59). Low renin hypertension is not always easy to differentiate from PA (60). Another study reported that 56% of 553 patients with primary aldosteronism had hypokalemia and 16% had cardio-and cerebrovascular comorbidities (30). A recent study investigated 327 people with hypertension and 90 control normotensive subjects with normal adrenal imaging. Serum aldosterone, active renin levels, aldosterone/active renin ratio were measured before and after a combined sodium chloride, fludrocortisone and dexamethasone suppression test (FDST). Post-FDST values were compared to cut-offs obtained from controls. Combined results of post-FDST aldosterone levels and ARR, revealed that 28·7% of the hypertensive patients had PA (61).

Screening for primary aldosteronism is generally recommended for patients with drug resistant hypertension, people with diuretic-induced or spontaneous hypokalemia, those with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age, and those with hypertension and an adrenal incidentaloma (35,62,63).

Genetic Insights into the Causes of Primary Aldosteronism

Recent advances in the genetics of PA have provided novel insights into the pathogenesis of unilateral forms of PA. Familial types of the disease have been described.

FAMILIAL HYPERALDOSTERONISM TYPE I (FH-I) OR GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM (GRA)

GRA (also known as familial hyperaldosteronism type I) is an autosomal dominant disorder characterized by a chimeric duplication, whereby the 5'-promotor region of the 11β-hydroxylase gene (regulated by ACTH) is fused to the coding sequences of the aldosterone synthase gene in a recombination event (gene defect in CYP11B1/CYPB2 -coding for 11beta-hydroxylase/aldosterone synthase). The result is that the aldosterone synthase gene (CYP11B2) is under the control of the promoter for the CYP11B1 gene, typically responsible for cortisol production under the regulation of ACTH. Aldosterone synthesis is therefore abnormally and solely regulated by ACTH (64,65). It leads to an ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin (49,66). The hybrid gene has been identified on chromosome 8. Under normal conditions, aldosterone secretion is mainly stimulated by hyperkalemia and angiotensin II. An increase of serum potassium of 0.1 mmol/L increases aldosterone by 35%. In familial hyperaldosteronism type 1 or glucocorticoid-

remediable aldosteronism, urinary hybrid steroids 18-oxocortisol and 18-hydroxycortisol are approximately 20-fold higher than in sporadic aldosteronomas. Intracranial aneurysms and hemorrhagic stroke are clinical features frequently associated with familial hyperaldosteronism type 1 (67). The diagnosis is made by documenting dexamethasone suppression of serum aldosterone using the Liddle's Test (dexamethasone 0.5 mg q 6h for 48h should reduce plasma aldosterone to nearly undetectable levels (below 4 ng/dl) or by genetic testing (Southern Blot or PCR) (68)(35).

FAMILIAL HYPERALDOSTERONISM TYPE II (FH-II)

It consists of a familial disease without unique phenotypic features or known genetic underpinnings), caused by mutations in the inwardly rectifying chloride channel CLCN2 (69) (70).

FH-III

FH-III (71) was associated with germline mutations in *KCNJ5*, a gene that encodes the inwardly-rectifying potassium channel GIRK4 (72) leading to an increase in aldosterone synthase expression and production of aldosterone (67). This type is characterized by severe childhood-onset hypertension, hypokalemia, remarkably high aldosterone-to-renin ratio, with marked adrenal enlargement and diffuse hyperplasia of the zona fasciculata.

This discovery set off international research efforts to investigate the role of potassium channel mutations in PA. Although the prevalence of *KCNJ5* germline mutations is considered to be extremely low (73–75), investigators have now reported the presence of *KCNJ5* somatic mutations in 30-50% of patients with APA's that were previously classified as sporadic (73,75–82). Hence, the discovery of a rare familial form of PA has resulted in the understanding that somatic potassium channel mutations may be a highly prevalent cause of PA. In general, from the reports to date, somatic mutations in *KCNJ5* appear to be associated with female gender, younger age, and higher aldosterone levels; however, these descriptions may reflect a significant sample selection bias.

Normally, adrenal zona glomerulosa cells maintain a hyperpolarized resting membrane potential that is largely regulated by potassium current. Depolarization of the cell (either by angiotensin II or hyperkalemia mediated inhibition of the potassium current) results in the opening of voltage-gated calcium channels, increased intracellular calcium signaling, and stimulation of aldosterone synthase. A gain-of-function mutation in GIRK4 results in sodium influx, cell depolarization, and increased aldosterone synthesis (83,84) (Figure 4-6). In this manner, mutations in channels that regulate the resting potential of zona glomerulosa cells have been implicated in the development of hyperaldosteronism. How these mutations may result in proliferation and adenoma production is not well understood. This understanding provoked further international collaborative research, especially among European research teams, to investigate the role of other cell membrane channels involved in maintaining zona glomerulosa cell resting potentials. This research has resulted in the discovery of somatic mutations in the sodium-potassium-ATPase, calcium-ATPase, and voltage-gated calcium channel all in the zona glomerulosa cell membrane in the pathogenesis of PA (70,85).

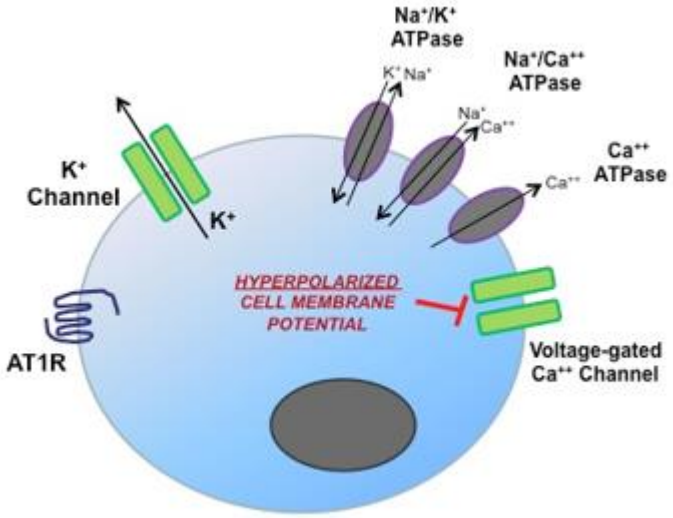

Figure 4. Adrenal zona glomerulosa cell membrane potential and KCNJ5 mutations. Normal resting equilibrium. The normal resting potential of zona glomerulsa cells is hyperpolarized thereby preventing calcium influx by inhibiting voltage-gated calcium channels.

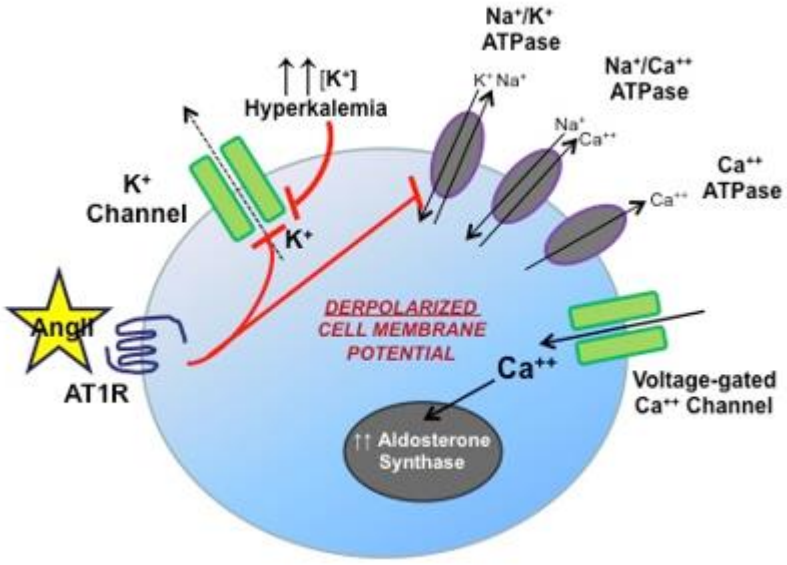

Figure 5. Adrenal zona glomerulosa cell membrane potential and KCNJ5 mutations. Normal aldosterone stimulation. Activation of the angiotensin receptor (ATR1) by angiotensin II (ANG II) or extracellular hyperkalemia results in depolarization of the cell and resultant calcium influx via activated

voltage-gated calcium channels. Calcium influx activates signaling to increase expression of aldosterone synthase and ultimately aldosterone production.

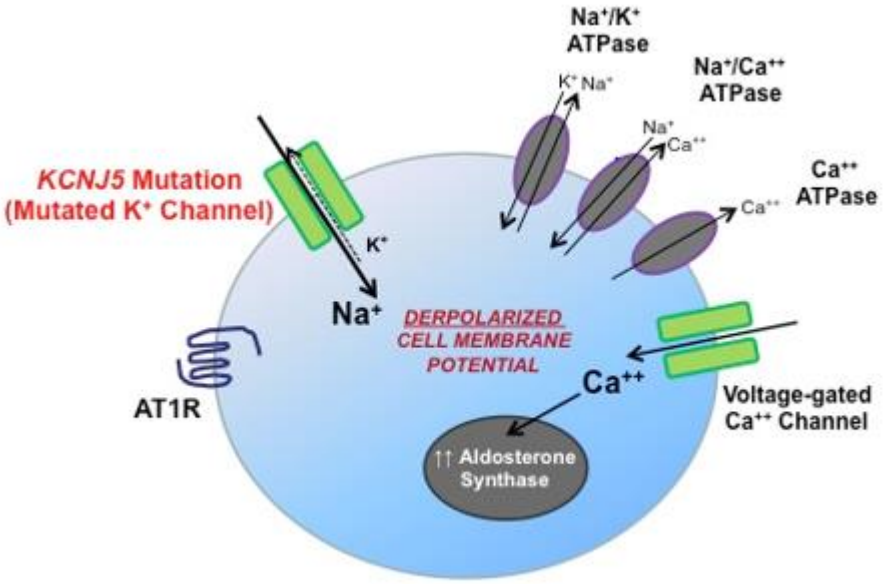

Figure 6. Adrenal zona glomerulosa cell membrane potential and KCNJ5 mutations. KCNJ5 mutations. Mutations in KCNJ5 result in permeability to Na^+, resultant depolarization and calcium influx via voltage-gated calcium channels. Similarly, mutant Na^+/K^+ ATPase and Ca^{++} ATPase result in cell membrane depolarization and calcium influx.

FAMILIAL HYPERALDOSTEREONISM TYPE IV (FH IV)

Familial aldosteronism type *IV* results from germline mutations in the T-type calcium channel subunit gene CACNA1H (86). Germline mutations in CACNA1D (encoding a subunit of L-type voltage-gated calcium channel $Ca_V1.3$) are found in patients with primary aldosteronism sometimes associated with seizures, and other neurological abnormalities (87).

With continued collaborative research, it is expected the number of mutated gene products regulating the resting potential of zona glomerulosa cells implicated in the pathogenesis of PA will grow. Whether the identification of these mutations will translate to treatment modalities remains to be seen.

Insights into the Syndrome of Subclinical Primary Aldosteronism

The histopathological discovery of aldosterone-producing cell clusters (APCCs), CYP11B2 expressing area and/or areas of abnormal foci of CYP11B2-expressing cells (6), sparked another leap in the understanding of PA pathogenesis (36,37). APCCs have now been identified in more than 50% of otherwise morphologically normal adrenal glands and are found with higher prevalence in older individuals (6). Recent studies reported decreased normal zona glomerulosa CYP11B2 expression and increased APCC expression with advancing age (6). Further, APCCs harbor somatic mutations known to increase autonomous aldosterone secretion in APAs

(37). Although studies of APCCs to date lack biochemical or clinical correlates to confirm that this histopathological phenotype of aldosterone synthase overexpression induces renin-independent aldosteronism, they raised speculation that the APCC may represent a precursor for development of APA or BAH. For example, APCCs exist even in adrenal tissue adjacent to an aldosterone-producing adenoma (36), suggesting that APCCs have non-suppressible aldosterone synthase activity. Several clinical studies to date have shown mild or "subclinical" renin-independent aldosteronism in normotensives and early stage hypertensives, and that this phenotype increases the risk for cardiometabolic disease (17,47,88–90); however, none of these clinical studies had histopathological evidence to link APCC's with the clinical phenotype. Therefore, future studies that integrate APCC histopathology with biochemical testing and incident clinical outcomes are needed to better characterize whether APCCs may represent the initial pathogenesis of PA (Figure 7).

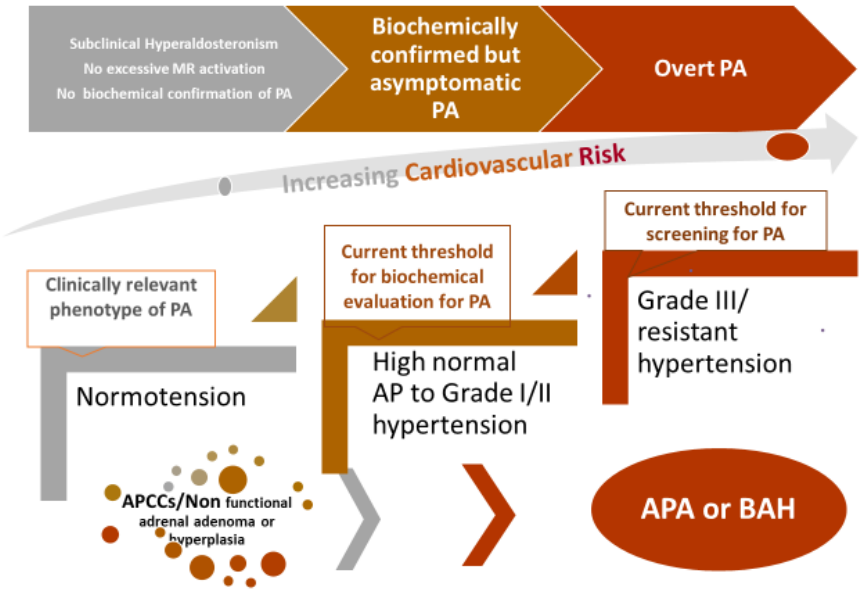

Figure 7. Phenotype and clinical manifestations of Primary aldosteronism (PA) varies. Current clinical practice guidelines recommend screening for primary aldosteronism using in Grade III or resistant hypertension. The patients with overt primary aldosteronism have the highest risk for incident cardiovascular disease. In milder forms of autonomous aldosterone secretion with biochemically confirmed primary aldosteronism, where arterial pressure may be normal- high normal or with grade I-II hypertension, populations for whom primary aldosteronism screening is not routinely recommended, have unrecognized, yet biochemically overt primary aldosteronism. In cases of subclinical primary aldosteronism, renin-independent aldosterone secretion can be seen among healthy normotensive populations with no obvious clinical syndrome of MR overactivation is apparent, but subtle biochemical evidence of renin-independent aldosteronism (plasma renin activity suppressed and inappropriately "normal" or high aldosterone levels). These people may be at higher risk for developing hypertension. Recent hypothesis suggests that the newly described non-neoplastic foci of CYP11B2-expressing cells called aldosterone-producing cell clusters (APCC) may represent a precursor to APAs or bilateral adrenal hyperplasia (BAH) (Vaidya et al., 2018)

Congenital Adrenal Hyperplasia

Another mineralocorticoid-excess state with low plasma renin activity is congenital adrenal hyperplasia (CAH). The most common cause of CAH is 21-hydroxylase deficiency, which can result in variable insufficiencies of cortisol and aldosterone. However, much rarer forms of CAH, for example, 11β-hydroxylase deficiency and 17α-hydroxylase deficiency can result in monogenic hypertension due to hypermineralocorticoidism, caused by elevated deoxycortisol and deoxycorticosterone levels, and resultant excessive mineralocorticoid receptor activation (91,92) (Figure 3).

Apparent Mineralocorticoid Excess (AME) and Liddle's syndrome

AME results from abnormal activation of the Type I mineralocorticoid receptor in the kidney by cortisol, secondary to an acquired (licorice ingestion or chewing tobacco) or congenital deficiency of the renal isoform of the type II isoenzyme of the corticosteroid 11-beta-dehydrogenase. This isoenzyme converts cortisol to the inactive cortisone in the renal distal convoluted tubule (91,93). However, in case of this isoenzyme's deficiency, the type I mineralocorticoid receptor is no longer 'protected' from activation by cortisol and responds to it as if it were aldosterone.

Mutations in 11β-hydroxysteroid dehydrogenase type 2 gene (*HSD11B2*) is a rare autosomal recessive disorder that is the main cause of AME, which is a form of low renin hypertension (94). The most common clinical manifestations are cardiovascular complications, severe hypertension, left ventricular hypertrophy, hypertensive retinopathy and nephrocalcinosis associated with hypokalemia. Death caused by cardiac arrest in adolescence has been reported (94).

In Liddle's syndrome, constitutive activation of the renal epithelial sodium channel (ENaC) results from activating mutations in the ENaC gene. In both AME and Liddle's syndromes, the intrinsic renal abnormalities described lead to unregulated and excessive sodium reabsorption, and therefore a biochemical phenotype of suppressed PRA, hypokalemia, and undetectable levels of plasma aldosterone (93).

CLINICAL FEATURES OF HYPERALDOSTERONISM

The clinical features of hyperaldosteronism are non-specific and variable, often resulting in or associated with hypertension. It is more important to distinguish whether the hyperaldosteronism is primary or secondary, as this pathophysiologic designation dictates the likely clinical syndrome (Table 1). Renal potassium wasting can result in hypokalemia. The phenotype depends largely on the underlying cause and the degree of the aldosterone excess, as well as the presence of other co-morbidities. The classic features of moderate-to-severe hypertension, hypokalemia, and metabolic alkalosis are highly suggestive of mineralocorticoid excess (usually primary aldosteronism). In the majority of cases, however, only subtle clues of hyperaldosteronism exist, such as the recent onset of refractory hypertension (defined as refractory to treatment with three classes of antihypertensives, including a diuretic) (43). Hypertension is common among patients with PA. Hypertension results from inappropriately high aldosterone secretion because

of plasma volume expansion and increased peripheral vascular resistance. Hypertension may be severe or refractory to standard antihypertensive therapies. However, some patients are normotensive or have minimal blood pressure elevations and, as a result, severe hypertension is not a *sine qua non* for this diagnosis (17,47,55,88,95).

Spontaneous hypokalemia in any patient with or without concurrent hypertension warrants consideration of hyperaldosteronism as the etiology. Additionally, patients that develop severe hypokalemia after institution of a potassium-wasting diuretic (such as hydrochlorothiazide or furosemide) should be investigated. It should be noted that in the majority of cases of PA serum potassium levels are normal (43,54).

PA results in extracellular volume expansion secondary to excess sodium reabsorption. However, after the retention of several liters of isotonic saline, an escape from the renal sodium-retaining actions of aldosterone occurs in part due to the increased secretion of atrial natriuretic peptide. Therefore, peripheral edema is rarely a feature of PA if cardiac and renal functions are normal.

Metabolic alkalosis occurs secondary to renal distal tubule urinary hydrogen ion secretion. It is usually mild, causing no significant sequelae, and may go unnoticed. Hypomagnesemia and mild hypernatremia (likely secondary to resetting of the osmostat) can also be observed.

Rarely, patients experience neuromuscular symptoms, including paresthesias or weakness, due to the electrolyte disturbances caused by the hyperaldosteronism. Nephrogenic diabetes insipidus, caused by renal tubule antidiuretic hormone resistance due to the hypokalemia, can cause nocturia and mild polyuria and polydipsia. Atrial fibrillation and cardiac arrhythmias may occur and can be life threatening.

Table 1. CLINICAL MANIFESTATIONS OF PRIMARY ALDOSTERONISM

Classic Manifestations
Hypertension 18-25%
Resistant Hypertension 8%
Hypokalemia (9 to 37%)
Hypervolemia
Metabolic alkalosis
Other Manifestations
Secondary to hypertension
Headaches female (57-59%) male (42-43%)
Retinopathy (rare)
Due to hypokalemia
Neuromuscular symptoms (cramps, paresthesias, weakness)
Nephrogenic diabetes insipidus
Cardiac arrhythmia (incl. atrial fibrillation)
Glucose intolerance / impaired insulin secretion

Secondary to direct actions of aldosterone on the cardiovascular system

Cardiac Hypertrophy/Fibrosis
Vascular smooth muscle hypertrophy

Secondary to a reset osmostat

Mild hypernatremia

DIAGNOSIS OF HYPERALDOSTERONISM

Secondary causes of hypertension (including hyperaldosteronism) should be considered initially in all hypertensive individuals. A thorough medical history and physical examination can greatly assist the clinician in deciding which patients should be further evaluated and what tests should be performed. Although the sensitivity of testing for hyperaldosteronism increases when limited to patients with moderate-to-severe hypertension, many patients with hyperaldosteronism have mild to moderate hypertension. The recent onset of refractory or accelerated hypertension, especially in a patient known to be previously normotensive, can be a valuable clinical clue. Therefore, the clinician must remain vigilant to the possibility of hyperaldosteronism, especially in the appropriate clinical setting.

Who to Screen for PA

The Endocrine Society has published clinical practice guidelines for the diagnosis and treatment of patients with PA (34). The task force recommends screening the following subtypes of patients deemed to be at high-risk for PA:

1. Patients with sustained blood pressure >150/100 mmHg on three or more measurements on different days.
2. Patients with hypertension resistant to three or more anti-hypertensive medications or patients requiring four or more anti-hypertensive medications to attain blood pressure control.
3. Patients with hypertension and sleep apnea.
4. Patients with hypertension associated with either spontaneous or diuretic-induced hypokalemia.
5. Patients with hypertension and an incidentally discovered adrenal adenoma.
6. Patients with hypertension with a family history of early-onset hypertension or cerebrovascular accident at age less than 40 years.
7. All hypertensive first-degree relatives of patients with PA, although there is insufficient data from prospective studies to support this recommendation.

GRA should be considered in patients with early-onset hypertension (<20yr) in the setting of a suppressed PRA. A family history of PA or early cerebral hemorrhage (<40yr) should also raise suspicion for GRA. Screening of GRA kindreds has revealed that most affected individuals are not hypokalemic (43,96).

How to Screen for PA

Evaluation for PA begins with hormonal screening, specifically determination of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) with validated, sensitive assays, for calculation of a plasma aldosterone to renin ratio (ARR). The use of automated direct renin concentration (DRC) rather

than PRA is increasing as automated DRC assays are becoming more available. In most studies, given that serum aldosterone is expressed ng/dL and plasma renin activity (PRA) in ng/mL per hour, an ARR > 20 is considered suspicious for PA (95% sensitivity and 75% specificity). When aldosterone is measured in pmol/L, ARR greater than 900 is consistent with primary aldosteronism. An ARR >30, especially in the setting of a PAC $\geq$ 15 ng/dL (555 pmol/L), has been shown to be 90% sensitive and 91% specific for the diagnosis of PA (29,43,97), whereas a ratio of >50 is virtually diagnostic of PA (97). The cut-off for ARR differs when using the DRC instead of PRA and differs further when employing SI units rather than conventional units (45). Interpretation of the ARR should be made after confirming that renin is suppressed in the setting of inappropriately high endogenous aldosterone production. The absence of renin suppression should raise suspicion for secondary aldosteronism and/or the use of medications that raise renin (mineralocorticoid receptor antagonists, renin inhibitors, renin-angiotensin-aldosterone system inhibitors, ENaC inhibitors, other diuretics that induce volume contraction).

To optimize the initial screening evaluation for PA, several aspects of the testing conditions must be considered (98). To begin with, the ARR is most sensitive when collected in the morning, after patients have been ambulatory for 2 hours, and have been seated for 5-15 minutes prior to blood drawing (43). Hypokalemia should also ideally be corrected prior to screening as it directly inhibits aldosterone secretion. Furthermore, drugs that alter aldosterone or renin secretion can result in false positive or false negative results. Beta-adrenergic blockers and central alpha agonists lower PRA secretion and often produce a false positive ARR in patients with essential hypertension. Diuretics, ACE-inhibitors (ACEI) and angiotensin receptor blockers (ARB) can increase PRA and result in false negative screening results. However, if the ARR while on any medication is high, with frankly elevated PAC and suppressed PRA, the likelihood of primary aldosteronism remains remarkably high. The mineralocorticoid receptor antagonists spironolactone and eplerenone, as well as renin inhibitors, can cause false negative ARR by virtue of raising the PRA. If a PRA is suppressed while on a mineralocorticoid receptor antagonist, the ARR may still be interpretable; however, in the context of an unsuppressed PRA, mineralocorticoid receptor antagonists should be discontinued for weeks-to-months until the PRA is suppressed, before the ARR is informative.

Understanding the impact of various medications on the ARR helps in the interpretation of results. When possible, it is ideal to withdraw the antihypertensive agents described above that affect the ARR 2-4 weeks prior to screening for PA; spironolactone and eplerenone, because of longer effect duration, should be stopped at least 4-6 weeks prior to testing. However, withdrawal of anti-hypertensives may not be feasible in patients with moderate to severe hypertension. Medications with neutral effects on the ARR, such as non-dihydropyridine calcium channel blockers, hydralazine, or alpha-blockers, can be used instead to control arterial pressure during the screening evaluation.

In addition to the ARR, new studies have implicated other biomarkers that may have a high sensitivity for screening PA. Titers of angiotensin II type I receptor autoantibodies are elevated in PA, and have been shown to exhibit discriminatory capability in distinguishing patients with APA, BAH, essential hypertension, and normotension (99). Additionally, emerging evidence has implicated a complex cross-talk between adrenal hormones and parathyroid hormone regulation (100,101); parathyroid hormone

levels may be able to distinguish those with PA from an APA (102).

Confirming the Diagnosis

In patients with a positive ARR, subsequent confirmation or exclusion of autonomous aldosterone secretion is necessary. Methods to demonstrate autonomy of aldosterone production focus on volume-expanding maneuvers. Options for volume expansion include oral sodium loading and intravenous saline infusion. Other confirmatory testing can be done by fludrocortisone suppression and captopril challenge (45). Combined fludrocortisone and dexamethasone suppression test and overnight diagnostic test using pharmaceutical RAAS (renin-angiotensin-aldosterone system) blockade with dexamethasone, captopril and valsartan (captopril was administered for inhibition of ACE activity, valsartan to counteract the remaining angiotensin activity and dexamethasone for suppression of the ACTH effect on aldosterone secretion) have also been suggested (103,104) (Table 2).

When prescribing the oral sodium loading test to confirm PA, patients should be instructed to consume a high sodium (200 mmol/day) diet for 4 days. This is best accomplished by adding 4 bouillon packets per day to a regular diet (each packet contains 1100 mg, or 48 mmol, of sodium). Sodium chloride tablets can also be used, though in our experience these may be poorly tolerated due to gastrointestinal upset. On the fourth day of high dietary sodium intake, a 24-hour urine collection for urinary aldosterone (or aldosterone excretion rate), creatinine, and sodium is collected. Oral salt loading should result in extra- and intra-vascular volume expansion and RAS suppression in normal individuals. Aldosterone excretion greater than 10-12 mcg/24h (ref. range <10 mcg/24h) in the presence of a urinary sodium excretion greater than 200 mmol/24 hours confirms the diagnosis of PA (45). The advantage of oral sodium loading is that it is easier for both the patient and clinician, as it can be performed on an outpatient basis without using hospital resources. However, this should not be performed on patients with severe uncontrolled blood pressure or moderate to severe, untreated hypokalemia. Blood pressure and potassium levels should be monitored during the testing, as hypertension and hypokalemia can be further precipitated or exacerbated with dietary sodium loading(43,105).

For the saline suppression test, 2 liters of isotonic saline are infused (500ml/h) over 4 hours. This test should not be performed in patients with compromised cardiac function due to the risk of pulmonary edema. Intravascular volume expansion should suppress the RAS. In normal subjects, PAC decreases below 5 ng/dL at the end of the saline infusion; levels greater than 10 ng/dL are considered diagnostic of autonomous aldosterone production. Values between 6 and 10 ng/dL are considered indeterminate (105,106).

Table 2. Tests to Confirm Primary Hyperaldosteronism

Confirmation Method	Protocol	Interpretation of Results
Oral Salt Suppression	·Increase sodium intake for 3-4 days via	· PA confirmed: if 24h urinary aldosterone excretion >12 mcg in setting of 24h sodium balance >200

Test	supplemental tablets or dietary sodium to >200 mmol/day · Monitor blood pressure · Provide potassium supplementation to ensure normal serum levels · Measure 24h urinary aldosterone excretion and urinary sodium on 3rd or 4th day	mmol · PA unlikely: if 24h urinary aldosterone excretion <10mcg
Intravenous Saline Infusion Test	· Infusion of 2L of normal saline after patient lies supine for 1 hour. · Infuse 2L of normal saline over 4 hours (500 mL/h) · Monitor blood pressure, heart rate, potassium · Measure plasma renin and serum aldosterone at time=0h and time=4h	· PA confirmed: 4h aldosterone level > 10 ng/dL · PA unlikely: 4h aldosterone level < 5 ng/dL
Captopril Challenge Test	· Administer 25-50mg of captopril in the seated position · Measure renin and aldosterone at time=0h and again at time=2h · Monitor blood pressure	· PA confirmed: serum aldosterone high and renin suppressed* · PA unlikely: renin elevated, and aldosterone suppressed* *varying interpretations without specific validated cut-offs
Fludrocortisone Suppression Test	· Administer 0.1 mg fludrocortisone q6h for 4 days · Supplement 75-100	· PA confirmed: Seated serum aldosterone > 6 ng/dL on day 4 with PRA< 1ng/mL/h · PA unlikely: suppressed aldosterone < 6 ng/dL

	mmol of NaCl daily to ensure a urinary sodium excretion rate of 3 mmol/kg/body weight · Monitor blood pressure · Provide potassium supplementation to ensure normal serum levels · Measure plasma renin and serum aldosterone in the morning of day 4 while seated	
Fludrocortisone-dexamethasone suppression test	Fludrocortisone-dexamethasone suppression test (FDST) (61) Administration of sodium chloride (2 g 3 times daily with food) plus oral fludrocortisone (0.1 mg every 6 h for 4 days) along with potassium gluconate (4.68 g three times daily) to maintain serum potassium within the normal range (3.5–5.5 mEql/l). At midnight on the 4th day 2 mg of dexamethasone are added (2 h after dinner)(12)	· PA confirmed: Upright plasma aldosterone > 82 pmol/l and ARR > 26 on day 5 at 0830 h (Simultaneous cortisol measurements (< 54 nmol/l) are required to confirm patients' compliance)
Recumbent post-low dose dexamethasone suppression (LDDST)-saline infusion test	Dexamethasone administration 2 mg/day (0.5 mg/6 h) for 2 consecutive days. Maintain recumbent position early in the morning of the 3rd day	· PA confirmed: Post-infusion plasma aldosterone <68 pmol/l and ARR < 10 pmol/mU

	(0830 h) and during the i.v. infusion of 2 l 0.9% normal saline over 4 h. Sampling for renin, aldosterone, cortisol and potassium drawn before initiation of infusion and after 4 h with continuous monitoring of BP and heart rate (12)	
Captopril-valsartan - dexamethasone test (103)	Day 1 at midnight, at least 2h after the last meal: 2mg dexamethasone, 50mg captopril, and 320mg valsartan. Day 2 morning: extra dose of 50mg captopril was given 1h before blood sampling, which was performed between 08:30 and 09:00 (cortisol, ALD, REN, ACTH, and potassium levels). All blood samples were drawn with the participants remaining seated in a non-stressful environment for at least 30 min.	· PA confirmed: Cutoff values of 0.3ng/dL/μU/mL (9pmol/IU) for ARR and 3.1ng/dL (85pmol/L) for aldosterone respectively

Identifying the Cause and Source of PA

Once the biochemical diagnosis of primary hyperaldosteronism has been confirmed, further testing is required to determine the etiology and identify the source of excessive aldosterone production. Distinguishing between APA, BAH, and less common forms of PA, such as GRA, is important. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH, and invariably reverses hypokalemia (38,107). In contrast, bilateral adrenalectomy in BAH cures hypertension in only <20% of patients (41,108). Hence, the treatment of choice is surgical in APA or UAH, and medical therapy is generally favored in BAH and GRA.

Biochemical characteristics can assist with the diagnosis of the various causes of PA. Age (<50 years old), severe hypokalemia (<3.0 mmol/L), high plasma aldosterone concentrations (> 25 ng/dl), and high urinary aldosterone excretion (>30 ug/24hr) favors the diagnosis of APA versus BAH. The presence of a classical unilateral Conn's adenoma in addition to a serum potassium < 3.5 mmol/L or estimated glomerular filtration rate > 100 mL/min/1.73 m^2 is nearly 100% specific for an APA. However, while sensitive or specific, these clinical tools lack validation in large cohorts, and therefore cannot be relied upon as a means to determine the underlying etiology in individual patients (40,43,97).

Patients with PA should undergo radiographic evaluation of the adrenal glands to localize the source and define the anatomy for potential surgical approaches. Computed tomography (CT) scanning with thin-slice (3mm) spiral technique is the best radiographic procedure to visualize the adrenal glands and serves primarily to exclude large masses that may represent adrenocortical carcinoma, which are usually more than 4 cm in size. Observation of a solitary hypodense adrenal nodule, usually < 2 cm in size, supports the diagnosis of APA. Adrenal adenomas typically are lipid-rich on CT scan (<10 HU) and have a greater than 50% washout of contrast after 10-15 minutes. However, even when biochemical features suggestive of APA are present, only one-third to one-half of patients have positive CT findings for a solitary adenoma (109,110). It is also not uncommon for both adrenal glands to be anatomically abnormal in patients with primary aldosteronism. Furthermore, it is emphasized that a radiographic abnormality does not correlate with a functional equivalent. Non-functioning adrenal 'incidentalomas' are not rare, especially in patients above the age of 40; these are radiographically indistinguishable from APA and can co-exist with an APA in the ipsilateral or contralateral adrenal gland. Recent studies suggest that Aldosterone-producing adenomas as well as non-functioning tumors are more likely to develop on the left side in patients with PA (111). However, data suggest that adrenal anatomy determined by CT scanning may wrongly predict etiology as well as lateralization of the aldosterone source in a significant proportion of patients (63,109).

Adrenal vein sampling (AVS) is a localization technique that is considered to be the 'gold standard' for distinguishing unilateral versus bilateral disease in PA. AVS involves sampling from the right and left adrenal veins, as well as from the inferior vena cava (IVC), for measurement of aldosterone and cortisol concentrations. Many favor performing AVS with adrenocorticotropin (ACTH) stimulation, which can be administered continuously or as a bolus, and may minimize stress-induced fluctuations in aldosterone secretion during the procedure as well as maximize aldosterone secretion from an APA (13,43,54,112). However, other studies indicate that ACTH does not significantly improve the diagnostic accuracy of the procedure, in part because it may increase secretion from the contralateral side more than from the APA itself and, therefore, blunts lateralization (13,113,114). It has been recently suggested that the use of cosyntropin stimulation can be justified only for centers with low experience to perform bilaterally simultaneous catheterization. In contrast, more experienced centers performing AVS should perform catherization studies to avoid the confounding effect that cosyntropin may have on lateralization (114).

Multiple variables derived from AVS can be used to determine lateralization of aldosterone hypersecretion (115). Cortisol-corrected aldosterone ratios (A/C ratio) are determined by dividing the aldosterone concentrations from each location sampled by the cortisol concentration in the same location to correct for dilutional effects. Recent

observational studies have also demonstrated that perhaps the most sensitive way to confirm contralateral suppression is when the ratio of the basal aldosterone concentration from the contralateral adrenal vein to the basal aldosterone concentration in the peripheral vein is less than 1.5 (13).

Using this approach, AVS has been reported to have a sensitivity of 95% and a specificity of 100% to detect unilateral disease (63). Adrenal vein sampling may not be necessary in patients with a high probability of APA by biochemical criteria, and a >1cm unilateral adrenal nodule with an anatomically normal contralateral gland if they are less than 40 years old (43,63). In all cases, if adrenal vein sampling is performed, it should be done by an experienced angiographer to increase the likelihood of a successful procedure (63).

There is a compelling argument against using adrenal venous sampling. Long considered the gold standard for localization and recommended by most experts and expert societies, adrenal venous sampling had never been tested in a randomized controlled trial until 2016. The “SPARTACUS” study was the first large randomized controlled trial to evaluate whether the use of adrenal venous sampling, when compared to decision making using the results of cross-sectional imaging, could influence clinical outcomes one year later (116). The study revealed no significant differences in antihypertensive medication needs or clinical manifestations for patients after 1 year of follow-up (116). Although medical therapy with an MR antagonist is the recommendation of choice for BAH, longitudinal and prospective studies dictating the optimal goals and targets to efficiently reduce cardiometabolic risk for these patients is lacking (45). Thus, this challenge to the long recommended liberal use of adrenal venous sampling suggests that empiric treatment with surgery or medication based on CT or MRI findings may yield an efficacious and cost-effective result (117,118). Several studies have debated the need for AVS or not and still no consensus has been obtained (119–122).

TREATMENT OF PRIMARY ALDOSTERONISM

Treatment for PA depends on the underlying etiology. The goals for optimal treatment are reduction of the adverse cardiovascular effects of chronic aldosterone excess, such as increased left ventricular mass increases/ stroke/ myocardial infarction/ heart failure and atrial fibrillation, normalization of the serum potassium and normalization of blood pressure, which often may persist after correction of the hyperaldosteronism.

Surgery is most often the treatment of choice for APA, and is often performed with laparoscopic techniques (anterior or posterior approaches) (123), which reduce patient recovery time and hospital cost. A newer treatment approach, and potential alternative to surgical resection, is radiofrequency ablation of a unilateral APA. Advances in imaging localization and radiofrequency techniques have demonstrated safe and effective ablations of APAs with long-term outcomes (with regard to blood pressure, potassium, and number of antihypertensives used) that are no different from surgical resection of APAs, but with arguably shorter hospital lengths of stay (124,125). However, several adverse effects have been reported, including hypertensive episodes, abdominal pain, hematuria, pancreatitis, pneumothorax, adrenal abscess formation, etc.(126–128). A clear advantage of radiofrequency ablation is the option to avoid surgery and instead pursue imaging guided needle placement and ablation; however, one clear disadvantage is the inability to obtain histopathology since the procedure destroys pathological tissue in situ. Resection or ablation of an APA may cure or

ameliorate hypertension, and invariably reverses hypokalemia. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH (39,108). Data suggests that resolution of hypertension after adrenalectomy for PA is less likely if there is family history of hypertension and use of two or more antihypertensive agents pre-operatively (21,41,107). Caution should be exercised in the perioperative and postoperative management of APA patients. Pre-operatively, hypertension and hypokalemia should be well controlled, which may require the addition of a mineralocorticoid receptor antagonist (45). Post-operatively, suppression of aldosterone secretion in the contralateral adrenal gland is expected and may result in a transient hyporeninemic hypoaldosteronism state. As a result, some patients exhibit post-operative salt wasting, mild hyperkalemia, and are at increased risk of dehydration and orthostatic hypotension if sodium restricted. Potassium and mineralocorticoid receptor antagonists should be withdrawn after surgery. PAC can be measured post-operatively as an indication of surgical response, however, re-equilibration of PRA post-operatively can take several weeks to months. Blood pressure tends to show maximal improvement 1-6 months post-operatively. For patients who are not operative candidates, or choose not to undergo surgery, medical management of hyperaldosteronism should be pursued (47), as described below for BAH.

BAH is best treated medically with the use of a mineralocorticoid receptor (MR) antagonist. However, it should be noted that in situations of grossly asymmetric BAH (where AVS indicates that one adrenal gland is clearly producing the vast majority of aldosterone), unilateral adrenalectomy can be considered to ‘debulk’ the major contributor to aldosterone excess if it may improve the patient’s quality of life or overall well-being. Although medical therapy with an MR antagonist is the recommendation of choice for BAH, longitudinal and prospective studies dictating the optimal goals and targets to efficiently reduce cardiometabolic risk for these patients is lacking (45). When medical therapy is pursued in the vast majority of BAH cases, the available options are the mineralocorticoid receptor antagonists eplerenone or spironolactone, which prevent aldosterone from activating the MR, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA (129). Spironolactone doses required are usually between 50 mg and 400 mg per day, usually administered once daily. The dose can be up-titrated every two weeks, until serum potassium values of 4.5 mEq/L are achieved. Studies have reported reductions in mean systolic and diastolic blood pressure of 25% and 22%, respectively (130,131). However, while it is effective for controlling blood pressure and hypokalemia, the use of spironolactone is limited by side effects. Gynecomastia and erectile dysfunction often occur during long-term treatment in males due to the anti-androgenic actions of spironolactone (132). The incidence of gynecomastia in males after 6 months of use at a dose of > 150 mg/d was as high as 52% (133). In women, spironolactone may lead to menstrual dysfunction, primarily intermenstrual bleeding. Fatigue and gastrointestinal intolerance are other common side effects. Eplerenone, which has similar antagonistic actions at the type I renal MR, has no anti-androgen activity since it does not bind to androgen or progesterone receptors, and therefore has fewer side effects. It is felt to have 60% of the MR antagonist potency of spironolactone (43). Eplerenone has a short half-life and is more effective if given twice daily. Its starting dose is 25 mg, twice daily. In order to achieve a sufficient response in PA, doses higher than 100 mg/day are often needed (134,135). A targeted mid- to high-normal serum potassium concentration without the aid of potassium supplements may suggest sufficient mineralocorticoid receptor blockade. A monitoring of plasma renin activity with an optimal value higher than 1

ng/mL/hour, has also been suggested to significantly reduce risk of major cardiometabolic events and mortality (28). Several studies reported that PA patients treated with high doses of MR antagonists, whose renin activity was increased, had significantly less risk for major cardiovascular events (atrial fibrillation, incident diabetes, myocardial infarction, heart failure hospitalization, or stroke and incident mortality). Importantly, the excess risk for these cardiovascular events, as well as death and atrial fibrillation was reduced, compared with primary aldosteronism patients treated with lower doses of MR antagonists, whose renin activity remained suppressed/undetectable. In these patients. An approximately three-fold excess risk for cardiovascular events and atrial fibrillation and a 63% higher risk for death were reported, when compared with age-matched patients diagnosed with essential hypertension (28,29,136). However, optimization with high dosage of MR antagonists may not be ideal in cases of glomerular filtration rate decline, when there is an increased risk of hyperkalemia with MR antagonist treatment (29).

When blood pressure is not controlled with spironolactone/eplerenone, or side-effects limit tolerability, the addition of other antihypertensive therapies may be required. Potassium-sparing diuretics, such as the ENaC inhibitors triamterene or amiloride, have been used, although they are usually not as effective as spironolactone (137). The dihydropyridine calcium channel antagonists have also been shown to effectively reduce blood pressure. Dietary sodium restriction (< 100 mmol/day), regular aerobic exercise, and maintenance of ideal body weight contribute to the success of pharmacologic treatment for hypertension in BAH (29). Novel treatment-agents, such as finerenone, a dihydropyridine-based nonsteroidal MR antagonist, are under evaluation for the treatment of PA. This newer MR antagonist has shown in preclinical studies, as well as in a phase I clinical trial, a beneficial and antifibrotic effect on cardiac and/or vascular activity, along with minimal side-effects regarding renal function and renal sodium and potassium homeostasis (138,139).

Glucocorticoid-remediable aldosteronism (GRA) can be successfully treated with low doses of glucocorticoids such as dexamethasone (96). By inhibiting ACTH release, the abnormal production of aldosterone can be suppressed. The lowest dose of glucocorticoid that can normalize blood pressure and potassium levels should serve to minimize side effects. PRA and PAC can be measured to assess treatment effectiveness and prevent overtreatment. The MR antagonists eplerenone and spironolactone are alternative treatments of hypertension in GRA (140).

CAUSES OF MINERALOCORTICOID EXCESS WITH HIGH PLASMA RENIN ACTIVITY (SECONDARY ALDOSTERONISM)

Secondary aldosteronism is the result of the hypersecretion of aldosterone because of increased activation of the renin-angiotensin system (RAS). The subgroups are best understood by contrasting the etiologies that usually produce hypertension from those that do not (Figure 3).

Usually Normo- or Hypotensive

The most common causes of secondary aldosteronism are medical illnesses that result from a reduction in perceived or effective circulating blood volume, such as congestive heart failure and nephrotic syndrome. Importantly, treatment and correction of the underlying medical illness and volume expansion results in reversal of the activated RAS. Secondary aldosteronism in a normotensive patient should also raise consideration for

Gittleman's and Barter's syndrome (see Figure 3 and further discussion in Hypertension section).

Diuretic use can also cause secondary aldosteronism. The findings can mimic those seen in renovascular hypertension, especially in a hypertensive patient. With chronic diuretic use, moderate to severe extracellular and intravascular volume depletion results in renal hypoperfusion, increased release of renin, and subsequently excessive aldosterone production. In rare occasions, surreptitious use of diuretics can produce misleading biochemical findings. A high degree of suspicion should be present in the appropriate setting, such as unexplained hypokalemia in a medical or paramedical worker or an individual attempting to lose weight using pharmacologic methods.

Usually Hypertensive

It is important to distinguish renal vascular disease from renal vascular hypertension. While a large proportion of the adult population may have renal vascular disease (defined as a 50% or greater decrease in renal artery luminal diameter), only a small portion of these patients experience critical and clinically relevant renal hypoperfusion and ischemia (141). Therefore, documentation of both structural and functional abnormalities is required before therapeutic intervention in such patients.

Renovascular hypertension is defined as hypertension associated with either unilateral or bilateral ischemia of the renal parenchyma. There are numerous causes of this disorder. Atherosclerosis of the renal arteries is the most common, accounting for 90% of cases. Fibromuscular dysplasia accounts for less than 10% of cases (141). In these disorders, decreased renal perfusion causes tissue hypoxia and decreased perfusion pressure, thereby stimulating renin release from the juxtaglomerular cells, resulting in secondary aldosterone secretion. Coarctation of the aorta can produce a similar pathophysiology due to renal hypoperfusion.

Although renal vascular hypertension can affect patients of all ages, it is commonly seen in older adults (>50 years) due to the increased prevalence of atherosclerosis in this population. When found in patients younger than 50 years of age, renal vascular hypertension is more common in women, usually as a result of fibromuscular dysplasia of one of both of the renal arteries (141,142).

In very rare cases, juxtaglomerular cell tumors of the kidney that hypersecrete renin have been described (143). Such patients often have severe hypertension, accompanied by marked elevation of renin and aldosterone levels, hypokalemia, and a mass lesion in the kidney. Confirmation includes documentation of unilateral renin secretion in the absence of renal artery stenosis. While rare, such cases are important to diagnose, as surgical removal of the tumor can be curative.

CLINICAL MANIFESTATIONS OF SECONDARY ALDOSTERONISM

Secondary causes of hyperaldosteronism have broad phenotypic variation and cannot be stereotyped by classical manifestations.

DIAGNOSIS OF SECONDARY ALDOSTERONISM

When there is clinical suspicion for renovascular hypertension, and initial screening has revealed a normal or elevated PRA, further testing for renovascular hypertension should be considered. Clinical features that should raise suspicion for renovascular hypertension include abrupt-onset hypertension, unexplained acute or progressive renal

dysfunction, renal dysfunction induced by renin-angiotensin-aldosterone system inhibitors, asymmetric renal dimensions, or suspicion of fibromuscular disease in a young patient. Importantly screening is only recommended if intervention will be pursued if a significant lesion is detected (142,144).

The diagnosis of renovascular hypertension requires two criteria: 1) the identification of a significant arterial obstruction (*structural* abnormality), and 2) evidence of excess renin secretion by the affected kidney (*functional* abnormality) (145). Structural abnormalities can be detected by a variety of imaging techniques. The gold standard is renal arteriography, but computed tomography (CT) scanning, duplex Doppler ultrasonography, and magnetic resonance angiography are reasonable non-invasive alternatives (142,144–146). Despite the multiple screening options, there is currently no single test that if negative completely excludes a stenotic lesion in the real arteries. Choosing among the various options is largely dependent on degree of clinical suspicion, availability of the technology, cost of the examination, and physician experience in performing and interpreting the results. The presence of renal insufficiency is an important consideration in determining the most appropriate diagnostic approach.

Evaluating the functional significance of a stenotic lesion in the renal arteries can be accomplished by captopril renography. For this procedure, 25-50 mg of captopril is administered one hour before a radioisotope is injected. Under normal conditions, administration of an ACE inhibitor reduces angiotensin II-mediated vasoconstriction and leads to relaxation of the efferent arteriole and an increase in glomerular filtration rate (GFR). This response is attenuated if the afferent blood flow is fixed by the presence of a stenotic lesion, and thus the difference between radioisotope excretion between the two kidneys is enhanced. Delayed excretion on the affected relative to the unaffected side provides functional evidence of renal artery narrowing (147). Although the captopril renogram is not recommended as a screening test for renal artery stenosis because of variable sensitivity and specificity depending on the populations studied (144), it is a tool for assessing the clinical significance of a stenotic lesion, and has high positive and negative predictive values for beneficial revascularization results (144).

TREATMENT OF SECONDARY ALDOSTERONISM

Renal artery stenosis is managed through medical therapy alone or combined with revascularization. The goal of treatment is blood pressure control, as well as prevention of decline in renal function and secondary cardiovascular disease (144,146). For renal artery fibromuscular dysplasia, primary angioplasty is the recommended endovascular procedure. In the case of atherosclerotic renovascular disease, angioplasty with stent placement is preferred over angioplasty alone, because data suggest improved outcomes in ostial renovascular stenosis. However, it must be noted that there is a paucity of level 1 data from randomized control trials demonstrating that revascularization has survival advantage in atherosclerotic renovascular disease (148). In all cases, an experienced interventional angiographer should perform angioplasty. Surgery for repair of renal vascular hypertension is reserved for patients with prior unsuccessful angioplasties.

Aggressive medical therapy should also be instituted and may be sufficient in many patients with atherosclerotic renovascular hypertension. Given the central role of the RAS in the pathophysiology of the disease, ACE inhibitors and ARB are the agents of choice for medical management and have anti-hypertensive as well as reno-protective effects.

Caution must be taken, however, as initiation of either agent can rarely be associated with precipitation of acute renal failure, particularly in patients who have critical, bilateral renal artery stenosis. As a corollary, acute deterioration of renal function after initiation of these medications in patients with hypertension should prompt clinicians to consider the diagnosis of bilateral renal artery stenosis (141,144).

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