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# Aldosterone and Cardiovascular Disease

Krishna K. Gaddam, MD, Eduardo Pimenta, MD,  
Saima Husain, MD, and David A. Calhoun, MD

**Abstract:** Aldosterone is an adrenal hormone that regulates sodium, fluid, and potassium balance. Jerome Conn first described the syndrome of autonomous and excessive aldosterone secretion or “primary aldosteronism.” Contrary to the historical belief, recent studies indicate that primary aldosteronism is a common cause of hypertension with a prevalence of 5-10% among general hypertensive patients. Various animal models have demonstrated that aldosterone in association with a high salt diet results in target-organ inflammation and fibrosis. Similarly, cross-sectional and observational human studies have demonstrated the association of aldosterone with development and severity of hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, and metabolic syndrome. Several interventional studies have also demonstrated the beneficial effects of mineralocorticoid receptor antagonists in these disease processes, particularly hypertension, heart failure, and post myocardial infarction, further supporting the role of aldosterone in their pathogenesis. We review the role of aldosterone in these various cardiovascular disease processes along with potential mechanisms and treatment. (Curr Probl Cardiol 2009;34:51-84.)

**T**he adrenal hormone aldosterone was first identified more than 50 years ago.<sup>1,2</sup> Studies done at the time had indicated that the hormone was produced in the zona glomerulosa of the adrenal

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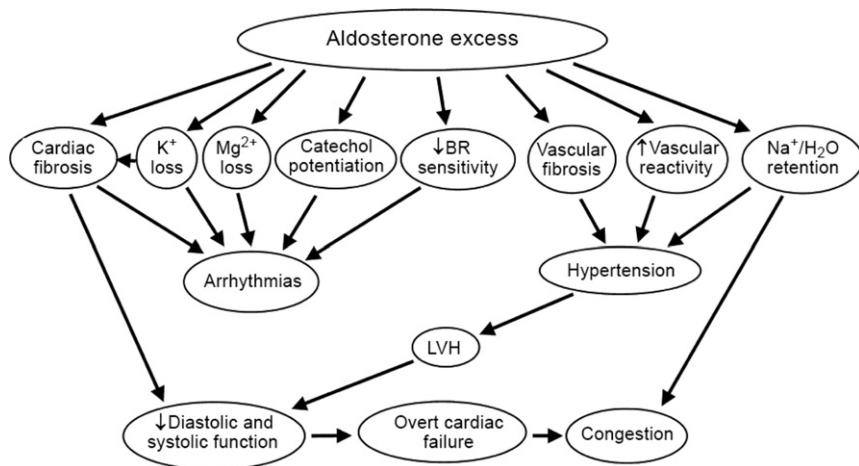
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gland largely in response to angiotensin II or high dietary potassium. The syndrome of autonomous and excessive aldosterone secretion secondary to an aldosterone-producing adrenal adenoma or “primary aldosteronism” (PA) was first described by Jerome Conn.<sup>3</sup> The index case of the syndrome was a young woman with severe hypertension, profound hypokalemia, and a pronounced metabolic alkalosis. She was eventually cured of the syndrome with removal of the aldosterone-producing adenoma by adrenalectomy. Early studies evaluating the prevalence of PA suggested that it was an uncommon cause of hypertension, being present in only 1-2% of hypertensive patients. More recent studies, however, indicate that PA is much more common than originally described with an estimated prevalence of 5-10% of the general hypertensive population<sup>4-7</sup> and approximately 20% of the patients with severe or resistant hypertension.<sup>8-12</sup>

The primary effect of aldosterone is to induce sodium and fluid retention, resulting in increases in intravascular volume. This effect occurs secondary to stimulation of cytoplasmic mineralocorticoid receptors in distal renal tubular cells, which results in an increase in the activity and number of epithelial sodium channels, thus promoting unidirectional transepithelial sodium transport.<sup>13,14</sup> In addition to this classical effect of aldosterone in causing sodium and fluid retention, experimental and human studies suggest that aldosterone, when in excess, separately has direct pro-inflammatory and pro-fibrotic effects contributing to target-organ deterioration as manifest by development of vascular, renal, and cardiac inflammation, fibrosis, and hypertrophy.<sup>15-18</sup> Consistent with these effects, increasing evidence links aldosterone excess and/or activation of mineralocorticoid receptor to the development and progression of various cardiovascular disease processes in humans including hypertension, coronary artery disease, congestive heart failure, chronic kidney disease, and the metabolic syndrome. In some cases, the underlying role of aldosterone in promoting cardiorenal disease has been confirmed with slowing or reversal of disease progression with preferential use of mineralocorticoid receptor antagonists.

## **Mechanisms of Aldosterone-Induced Cardiovascular Disease**

Aldosterone likely promotes development and/or progression of cardiovascular disease through multiple mechanisms including chronic intravascular fluid retention, suppression of endothelial function, and induction of target-organ inflammation and fibrosis. First, the classical effect of aldosterone excess in causing inappropriate volume retention contributes



**FIG 1.** Proposed mechanisms by which aldosterone excess may bring about adverse cardiovascular sequelae. BR, baroreceptor; LVH, left ventricular hypertrophy. (Reprinted with permission from Stowasser M. New perspectives on the role of aldosterone excess in cardiovascular disease. *Clin Exp Pharmacol Physiol* 2001;28:783-91.)

directly to increases in blood pressure (BP), cardiac output, intracardiac volumes, and glomerular filtration rate. An increase in intravascular volume results in increases in BP, which in turn contributes to increased risk of stroke, heart disease, and chronic kidney disease. Chronic increases in intracardiac volumes, particularly in the setting of uncontrolled hypertension, would be anticipated to increase risk of developing heart failure, while increases in left atrial volume would predispose to development of arrhythmia, particularly atrial fibrillation. Increases in circulating volume also result in increases in renal plasma blood flow. The associated increases in intraglomerular pressure and glomerular filtration rate contribute to glomerular dysfunction as indicated by increases in proteinuria. Other possible effects of aldosterone that may contribute to the pathogenesis of cardiovascular disease include increases in sympathetic activation, impairment of baroreflex function, and increases in thrombogenesis (Fig 1).<sup>19</sup>

A growing body of evidence suggests that aldosterone, independent of its effects on BP and intravascular volume, impairs vascular function through suppression of nitric oxide formation and increases in reactive oxygen species. Aldosterone added to rat vascular smooth muscle cells *in vitro* inhibits expression of inducible nitric oxide synthase that is stimulated by interleukin-1 $\beta$  in a dose-dependent fashion.<sup>20</sup> In a rat model

of heart failure, spironolactone, a nonselective mineralocorticoid receptor antagonist, added to an angiotensin-converting enzyme inhibitor (ACEI), improves endothelium-dependent aortic ring relaxation, presumably by suppressing formation of superoxide anion ( $O_2^-$ ), a potent scavenger of nitric oxide.<sup>21</sup> Eplerenone, a selective mineralocorticoid receptor antagonist, has a similar effect on  $O_2^-$  production in experimental models of atherosclerosis.<sup>22</sup>

Assessments of vascular compliance or forearm blood flow link chronic aldosterone excess with endothelium-dependent vascular dysfunction in humans. In subjects with hypertension<sup>23</sup> or heart failure,<sup>24</sup> plasma aldosterone correlates negatively with systemic arterial compliance as calculated from intraarterial BP and cardiac output. In subjects with primary and secondary (ie, renovascular hypertension) hyperaldosteronism, forearm blood flow response to acetylcholine, an endothelial-dependent vasodilator, as assessed by venous occlusion plethysmography is reduced.<sup>25</sup> Similarly, use of venous plethysmography to assess forearm blood flow in subjects with chronic heart failure suggests that spironolactone, added to chronic angiotensin converting enzyme (ACE) inhibition, improves endothelial function secondary to increased nitric oxide availability.<sup>26</sup>

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**Jay Cohn:** The study by Duprez et al (ref. 24) is misrepresented. Large artery compliance was measured with a noninvasive radial pulse contour methodology that separates large-artery from small-artery compliance or elasticity. The correlation between aldosterone levels and reduced large-artery compliance suggests a long-term structural effect on large arteries, perhaps through collagen growth. Endothelial dysfunction does not directly affect the large arteries but it does affect the small arteries (Gilian M, Kaiser DR, Bratteli CW, et al. Role of nitric oxide deficiency and its detection as a risk factor in pre-hypertension. *J Am Soc Hypertens* 2007;1(1):45-55).

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In a recent study by our laboratory, we demonstrated that flow-mediated, endothelium-dependent vascular reactivity of the brachial artery was significantly correlated with both plasma aldosterone and 24-h urinary aldosterone excretion in patients with resistant hypertension, suggesting that aldosterone excess contributes directly to endothelial dysfunction.<sup>27</sup> This impairment in endothelial-dependent vascular reactivity was reversed, in large part, with chronic mineralocorticoid receptor antagonism with administration of spironolactone. This improvement with spironolactone treatment occurred in subjects maintained on an ACEI or angiotensin receptor blocker (ARB),

indicating endothelial benefit in addition to that accomplished by inhibiting ACE or blocking the angiotensin II type I receptor.

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**Jay Cohn:** Although these conjectures are attractive, it may be oversimplified to identify aldosterone as the culprit. The levels of aldosterone associated with these clinical syndromes are only modestly increased, usually to levels lower than associated with salt restriction in normal subjects. Does salt restriction lead to endothelial dysfunction? ACE inhibitors and ARBs have additive effects on suppressing aldosterone levels (Cohn JN, Anand IS, Latini R, et al, for the Val-HeFT Investigators. Sustained reduction of aldosterone is response to the angiotensin receptor blocker valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. *Circulation* 2003;108:1306-9), and aldosterone receptor antagonists interfere with the action of other steroid hormones as well (Stewart PM, Corrie JE, Shackleton CH, et al. Syndrome of apparent mineralocorticoid excess: a deficit in the cortisol-cortisone shuttle. *J Clin Invest* 1988;82:340-9). Cause and effect is not as simple and clear-cut as the authors suggest.

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Prospective evaluations have shown that impaired endothelial function as indicated by assessment of brachial artery forearm blood flow is associated with an increased incidence of cardiovascular disease.<sup>28</sup> Taken in consideration with the above findings linking aldosterone excess to impairment of endothelial function, it suggests that aldosterone-induced endothelial dysfunction underlies, at least in part, aldosterone-associated increases in cardiovascular risk.

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**Jay Cohn:** This is a satisfying hypothesis because of the growing evidence that endothelial dysfunction underlies progressive atherosclerosis, but the pathophysiologic effects of aldosterone on endothelial dysfunction will require careful prospective study, perhaps with infusion of aldosterone in normal subjects, to document a dose-dependent effect on endothelial function and nitric oxide bioavailability.

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Multiple studies have confirmed a direct effect of aldosterone in causing target organ inflammation and fibrosis. These pro-inflammatory and pro-fibrotic effects of aldosterone occur independent of increases in BP and are prevented with mineralocorticoid receptor antagonists such as spironolactone or eplerenone.<sup>15-18</sup> Beginning with seminal studies by Brilla and Weber, rat models of hyperaldosteronism have demonstrated aldosterone-induced heart, kidney, and brain deterioration that manifests initially as perivascular inflammation that progresses to fibrosis with broad extension beyond the perivascular regions if the aldosteronism is maintained.<sup>16</sup> In the case of the heart, the inflammatory and fibrotic

lesions also occurred on the right side of the heart where intravascular pressures remained low, indicating that the tissue effects were not secondary to increases in BP. In these and other studies, blockade of the experimentally induced inflammation and fibrosis with mineralocorticoid receptor antagonists confirmed the role of aldosterone as the underlying cause of the target-organ lesions.

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**Jay Cohn:** Because of the other hormone-inhibiting actions of aldosterone antagonists, it is dangerous to attribute all the effects of these drugs to aldosterone inhibition.

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In animal studies of hyperaldosteronism, aldosterone-induced inflammation and fibrosis occurred only if there was concomitant high dietary salt intake, indicating that the combined effects of aldosterone excess and high salt ingestion were necessary for induction of the target-organ damage. In one of the earliest demonstrations of this interaction, Brilla and Weber found that the myocardial fibrosis observed in experimentally induced hyperaldosteronism was prevented equally well either by spironolactone or by maintenance of a low salt diet.<sup>16</sup> The obligatory role of high salt diet in actualizing the deleterious effects of aldosterone has been confirmed by other investigators.<sup>17,18</sup> Combined, these results emphasize the important role of dietary sodium excess in contributing to cardiovascular risk and the potentially beneficial role of dietary salt restriction in terms of broadly reducing cardiovascular complications.

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**Jay Cohn:** What is the mechanism of the interaction between aldosterone and sodium? Sodium excess alone can induce cardiovascular lesions (Limas C, Westrum B, Limas CJ, et al: Effect of salt on the vascular lesions of spontaneous hypertensive rats. *Hypertension* 1980;2:477-89). It is the sodium or the aldosterone?

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## Aldosterone and Hypertension

It was reported more than 50 years ago by Genest et al that mild hyperaldosteronism is a frequent finding in patients with presumed primary hypertension.<sup>29</sup> More recently, cross-sectional and prospective studies have indicated that aldosterone contributes significantly to both the development and the severity of hypertension as well as to resistance to antihypertensive treatment. These effects have been described in normotensive and general hypertensive populations separate from the presence of

classically defined PA. In a recent prospective analysis that included 1688 normotensive participants in the Framingham Offspring Study,<sup>30</sup> serum plasma aldosterone levels within the physiologic range predicted subsequent increases in BP defined as an increment of at least one BP category (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure or JNC VI) as well as the development of incident hypertension defined as a systolic BP of  $\geq 140$  mm Hg or a diastolic BP  $\geq 90$  mm Hg or the use of antihypertensive medications. Plasma renin activity (PRA) was not measured in these subjects. During a 4-year follow-up, a 16% increase in the risk of an elevation in BP and a 17% increase in the risk of hypertension were observed per quartile increment in the serum aldosterone level. There was a 1.60-fold increased risk of a significant increase in BP and a 1.61-fold increase risk of developing hypertension in the highest serum aldosterone quartile compared to the lowest quartile.

In a separate analysis by the Framingham investigators, the combined effects of plasma aldosterone and plasma renin activity (as indexed by the aldosterone/renin activity ratio) as a predictor of BP progression and incident hypertension was assessed.<sup>31</sup> The prospective evaluation included 3326 nonhypertensive participants in the Framingham Heart Study. During follow-up (mean of 3 years), 34% of the subjects had significant progression of their BP ( $\geq 1$  JNC VI blood pressure category) and 16% developed hypertension. The rates of BP progression and hypertension incidence rose across aldosterone/renin ratio quartiles in graded fashion and in multivariable analysis; each standard deviation increment in aldosterone/renin ratio was associated with a 23% increased risk of BP progression and a 16% increased risk of developing hypertension. Strikingly, the top aldosterone/renin ratio quartile was associated with an 89% increased risk of BP progression and a 53% increased risk of hypertension compared to the lowest aldosterone/renin ratio quartile. In this analysis, renin activity was inversely related to BP regression and hypertension incidence, but with only the latter being statistically significant. That is, increased risk of BP progression and development of hypertension was associated with lower values of the renin activity.

The results of these two studies strongly implicate aldosterone, whether considered separately or in the context of low renin activity as an important cause of worsening of BP levels and development of incident hypertension. In these analyses, the effects of aldosterone and renin activity were in opposite direction, with high levels of the former and low levels of the latter predicting increasing BP. Overall, these results suggest that, in the general population, increasing aldosterone levels contribute

importantly to progressive fluid retention (as indicated by corresponding decreases in renin activity) and consequent increases in BP. Whether early use of low doses of mineralocorticoid receptor antagonists and/or dietary salt restriction might broadly prevent development of hypertension has not been studied.

In a cross-sectional evaluation that compared normotensive and hypertensive black American and white French Canadian subjects, hypertensive subjects had higher supine and standing aldosterone and lower renin levels compared to normotensive subjects.<sup>32</sup> Supine and standing plasma aldosterone levels were significantly related to daytime and nighttime systolic and diastolic BP levels in the African American subjects. In the French Canadian subjects, standing aldosterone levels correlated with daytime and nighttime diastolic BP levels, while supine aldosterone levels correlated only with nighttime systolic BP. No consistent correlations were noted between plasma renin activity and BP in either group, suggesting that aldosterone, more so than renin-angiotensin II, contributed to the severity of hypertension. These results complement the findings from the Framingham investigators, in linking plasma aldosterone levels to the severity of hypertension.

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**Jay Cohn:** Is the primary effect of aldosterone to raise blood pressure, or is its effect on the small artery to reduce its compliance and thicken its wall, resulting in a rise of blood pressure as a secondary mechanism?

The data on renin suggesting low renin levels associated with worse disease stands in direct conflict with the data from Alderman and Laragh identifying high renin as associated with cardiovascular morbid events (Alderman MH, Ooi WL, Cohen H, et al. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens* 1997;10:1-8).

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### *Primary Aldosteronism and Hypertension*

Although Dr. Conn speculated that the prevalence of PA might be as high as 20% in patients in patients with hypertension,<sup>33</sup> for several decades afterwards studies suggested that PA was an uncommon cause of hypertension with an estimated prevalence of no more than 1-2% among general hypertensive populations.<sup>34</sup> However, recent studies from various laboratories worldwide have been consistent in suggesting that the prevalence of PA is considerably higher than the 1-2% reported historically. Gordon and colleagues, in Brisbane, Australia, were the first to suggest an increased prevalence of PA in reporting that approximately 12% of unselected, normokalemic hypertensive patients had PA based on a high



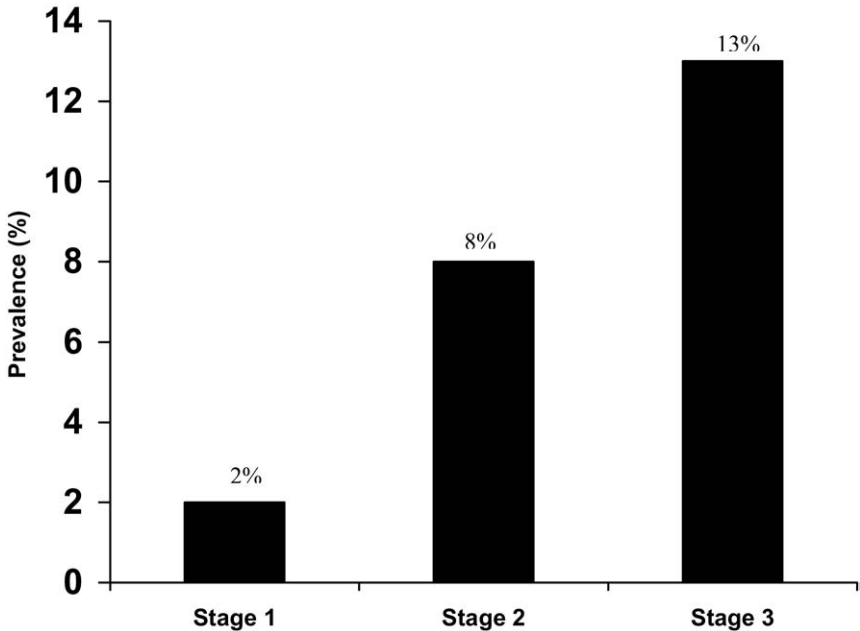
aldosterone renin ratio (ARR) and failure to suppress plasma aldosterone levels with volume expansion (ie, fludrocortisone acetate administration and oral salt loading).<sup>35,36</sup> Subsequently, multiple studies have confirmed that PA is common with a prevalence of 5-10% among unselected hypertensive patients<sup>4-7</sup> and 15-20% in patients with resistant hypertension.<sup>8-12</sup>

Two recent studies highlight aldosterone excess as a common cause of hypertension. Schwartz and Turner determined the prevalence of PA in 118 white subjects with primary hypertension.<sup>7</sup> Subjects with resistant hypertension (use of >3 antihypertensive agents) were excluded. The evaluation was extremely rigorous in that all subjects were assessed after being withdrawn from antihypertensive therapies and suppression testing was done in all subjects with 4 days of dietary salt loading. Based on failure of dietary salt loading to suppress urinary aldosterone excretion to <12  $\mu\text{g}/24\text{ h}$ , 13% of subjects were diagnosed with PA, confirming a very high prevalence of PA in subjects with uncomplicated mild/moderate hypertension.

In an earlier study, Mosso et al screened over 600 hypertensive patients with an ARR.<sup>6</sup> Subjects with a high ARR (>25) underwent suppression testing with 4 days of dietary salting loading and fludrocortisone administration. PA was diagnosed with failure of the serum aldosterone to suppress to <5 ng/dL. This study was particularly informative in that the severity of the untreated hypertension based on JNC VI stages (stage 1, 140-159/90-99, stage 2, 160-179/100-109, stage 3,  $\geq 180/110$  mm Hg) was known for each subject. The investigators were therefore able to relate the prevalence of PA to the severity of the underlying hypertension. The overall prevalence of PA was 6.1%. The prevalence, however, increased progressively with severity of hypertension. In subjects with stage 1 hypertension, the PA prevalence was only 2%; in subjects with stage 2 hypertension, the PA prevalence was 8%, and in subjects with stage 3 hypertension, the prevalence was 13%. The results demonstrate that the likelihood of PA increases with increasing severity of hypertension such that patients with mild hypertension are at low risk, while patients with severe hypertension are at high risk of having PA (Fig 2).

In the above two studies and in the almost all recent screenings for PA, hypokalemia was usually not present in patients diagnosed with PA. In the Mosso et al study, only 1 or 2.7% of the 37 subjects confirmed to have PA were hypokalemic.<sup>6</sup> In the Schwartz and Turner study, hypokalemia excluded enrollment so that none of the subjects diagnosed with PA presented with hypokalemia.<sup>7</sup> These results emphasize that hypokalemia is not an obligatory manifestation of PA and, in fact, is not present in most patients with demonstrable aldosterone excess. This observation is consistent with

## Prevalence of Primary Aldosteronism According To Hypertension Severity



**FIG 2.** Prevalence of primary aldosteronism in patients. Sixth Joint National Committee (JNC VI) stages of severity of hypertension (stage 1, 140-159/90-99 mm Hg; stage 2, 160-179/100-109 mm Hg; stage 3,  $\geq 180/110$  mm Hg). (Adapted with permission from Mosso L, Carvajal C, Gonzalez A, et al. Primary aldosteronism and hypertensive disease. *Hypertension* 2003; 42:161-5.)

Jerome Conn's eventual opinion that hypokalemia was not always present in subjects with PA and instead was a late manifestation of the disorder.<sup>33</sup>

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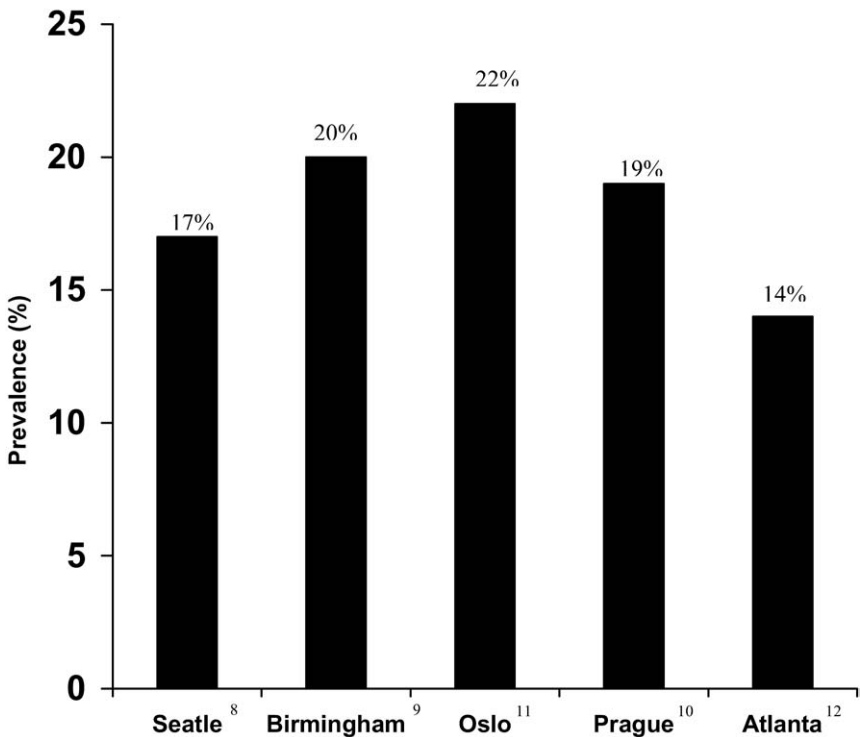
**Jay Cohn:** The tradition is to use arbitrary cut-points, such as blood pressure and blood sugar, to define disease. However, we know that all such measurements represent a continuum. Rather than label a specific cut-point as PA, perhaps it would be more informative to view the syndrome as a continuum from absent to mild to severe, with a mechanism (eg, the classical idea of an adenoma) often unknown.

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### *Primary Aldosteronism and Resistant Hypertension*

PA is particularly common in patients with resistant hypertension. In an evaluation of 88 consecutive patients referred to the hypertension clinic at

### Prevalence of Primary Aldosteronism in Subjects with Resistant Hypertension



**FIG 3.** Prevalence of primary aldosteronism in patients with resistant hypertension from multiple clinics worldwide. [Compiled from refs.<sup>8-12</sup>]

the University of Alabama at Birmingham, PA was diagnosed in 20% of consecutive patients referred for resistant hypertension, defined as hypertension requiring three or more different antihypertensive medications.<sup>9</sup> PA was diagnosed by a suppressed plasma renin activity ( $<1.0$  ng/mL/h) and elevated urinary aldosterone ( $>12$   $\mu$ g/24 h) in the setting of high dietary sodium ingestion ( $>200$  mEq/24 h). In this study, suppression testing was done in all evaluated patients. A similarly high occurrence of PA in patients with resistant or poorly controlled hypertension was observed in separate studies by investigators in Seattle, Washington<sup>8</sup>; Prague, Czech Republic<sup>10</sup>; Oslo, Norway<sup>11</sup>; and most recently, Atlanta, Georgia,<sup>12</sup> indicating that aldosterone excess commonly underlies resistance to antihypertensive treatment (Fig 3).

In a study that included 157 hypertensive patients and elevated plasma aldosterone ( $\geq 12$  ng/dL) and ARR ( $\geq 25$ ) and 160 hyperten-

sive patients with normal or low plasma aldosterone levels (<12 ng/dL), Sartori et al reported that the patients with high aldosterone levels irrespective of the presence or absence of PA had more severe hypertension and took longer to achieve goal BP despite intensive treatment, further supporting the role of aldosterone excess as an important cause of resistant hypertension.<sup>37</sup>

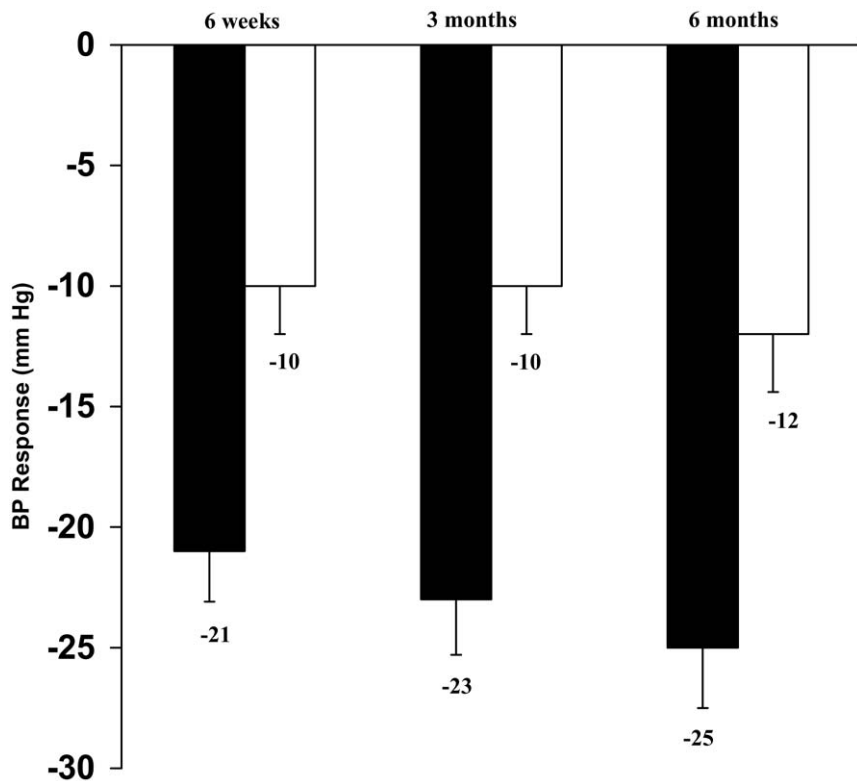
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**Jay Cohn:** The transition in thinking about PA is dramatic. In earlier days PA was viewed as causing a more mild form of hypertension with lower risk of morbid events (Tarazi RC, Ibrahim MM, Bravo EL, et al. Hemodynamic characteristics of primary aldosteronism. *N Engl J Med* 1973;289:1330).

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Concomitant with reports indicating that PA is a common cause of resistance to treatment were studies describing the antihypertensive benefit of mineralocorticoid receptor antagonists in treating resistant hypertension.<sup>38-41</sup> In an open-label evaluation done by our laboratory, the antihypertensive benefit of spironolactone 25-50 mg was prospectively assessed when added to the existing regimen of subjects whose BP was uncontrolled on three or more antihypertensive agents.<sup>39</sup> A total of 76 subjects, including an equal number of African American and white subjects, were included in the analysis. Subjects were on an average of four medications including a diuretic and an ACEI or an ARB. The mean daily dose of spironolactone at study end (6 months) was approximately 31 mg, so the majority of subjects remained on 25 mg. At 6 months follow-up, the mean BP reduction was  $25 \pm 20/12 \pm 12$  mm Hg (Fig 4). The BP reduction induced by spironolactone was similar in African American and white subjects. Interestingly, the BP reduction was not predicted by plasma aldosterone, renin activity, or 24-hour urinary aldosterone excretion. That is, subjects with high versus normal or low aldosterone levels responded equally well, although subjects with hyperaldosteronism were more likely to be titrated to the 50 mg dose of spironolactone.

Mahmud et al evaluated the BP response to adding 50 mg of spironolactone to the regimen of patients whose BP was uncontrolled on three agents.<sup>40</sup> At 14 weeks of follow-up, the mean BP reduction was  $28 \pm 3/13 \pm 2$  mm Hg. In this study, the BP response was also not predicted by the baseline ARR. However, in a separate analysis of patients untreated with other antihypertensive medications, the ARR was predictive of the BP reduction induced by spironolactone. This differential relationship between the baseline ARR and response to aldosterone



**FIG 4.** Spironolactone-induced reduction in systolic blood pressure (BP) (filled bars) and diastolic BP (open bars) at 6 weeks, 3 months, and 6 months follow-up in subjects with resistant hypertension ( $n = 76$ ). (Reprinted with permission from Nishizaka MK, Zaman MA, Calhoun DA. Adapted with permission from Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003;16:925-30.)

blockade in treated versus untreated subjects suggests two possibilities that may be contributing to the discrepancy: (1) a greater role of aldosterone in causing resistant hypertension than is reflected by plasma levels and/or (2) the effects of antihypertensive medications on the ARR alter its predictive value in relation to the BP response to mineralocorticoid receptor blockade.

Data from Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm also demonstrated a significant BP lowering effect of spironolactone when prescribed to patients whose BP was uncontrolled on three or more antihypertensive medications.<sup>41</sup> Spironolactone 25-50 mg reduced systolic and diastolic BP by 21.9 and 9.5 mm Hg, respectively. This study was particularly compelling in demonstrating the benefit of

spironolactone in treating resistant hypertension in that it was a prospective, multicenter evaluation that included more than 1400 participants who maintained this level of BP reduction for at least a year.

Other investigators have described the benefit of amiloride as add-on therapy in treating resistant hypertension. By blocking the epithelial sodium channel, amiloride acts as an indirect aldosterone antagonist as aldosterone induces sodium and fluid retention, in part, through up-regulation of the epithelial sodium channel. Eide et al evaluated the BP response of adding amiloride 2.5 mg to existing multidrug regimens, including a diuretic, in subjects with resistant hypertension.<sup>11</sup> Thirty-eight subjects, all of whom had suppressed renin activity at baseline, were included in the analysis. After 2 weeks of treatment, mean BP was reduced by  $31 \pm 31/15 \pm 11$  mm Hg. In a subset of 26 subjects, after doubling the amiloride/diuretic dose, an additional reduction in systolic and diastolic BP of 11 and 4 mm Hg, respectively, was observed.

Saha et al compared the BP effects of amiloride 10 mg daily, spironolactone 25 mg daily, or a combination of both agents when used as add-on therapy in African American subjects whose BP was uncontrolled on a two-drug regimen consisting of a diuretic and a calcium channel blocker.<sup>42</sup> Ninety-eight subjects were randomized between the three treatment groups or placebo in a  $2 \times 2$  factorial design with a treatment period of 9 weeks. The systolic and diastolic blood pressures decreased an average of  $12.2 \pm 2.2/4.8 \pm 1.3$  mm Hg in amiloride arm,  $7.3 \pm 2.3/3.3 \pm 1.4$  mm Hg in spironolactone arm, and  $14.1 \pm 2.3/5.1 \pm 1.4$  mm Hg in the combination arm versus placebo. Although amiloride was somewhat better than spironolactone in reducing BP, it was noted that amiloride use was associated with significant increases in PRA, while spironolactone was not, suggesting that the spironolactone may have been under-dosed, such that, with further up-titration, additional BP benefit might have been observed.

## **Why the High Prevalence of Primary Aldosteronism?**

Why PA is seemingly so much more common now than reported historically is unknown. It is likely that PA was previously underestimated as early evaluations of prevalence were often limited to patients presenting with hypokalemia, which is now recognized as a late manifestation of the disorder. Further, screenings of large numbers of subjects for PA was facilitated by standardization of aldosterone and renin activity measurements as well as by recognition of the diagnostic screening value

of the ARR. These technical advancements allowed for screening of larger, unselected cohorts as opposed to assessments of small numbers of patients at high risk of having severe disease. Consequently, in screening much broader cohorts, earlier and/or milder manifestations of the disease are identified.

Like classically described PA, the aldosterone excess being described today seems to occur independent of renin-angiotensin II as high aldosterone levels are not related to concomitant measurements of PRA. While stimuli that underlie the increasing occurrence of hyperaldosteronism remain to be elucidated, recent studies suggest that obesity may be an important contributing factor. Biopsies of human adipose tissue indicate reduced activity of the renin-angiotensin system within adipocytes with weight loss.<sup>43</sup> Separately, factors isolated from human adipocytes have been shown to function as aldosterone secretagogues independent of renin-angiotensin.<sup>44,45</sup> Last, preliminary data link aldosterone levels to severity of obstructive sleep apnea in subjects with resistant hypertension.<sup>46</sup> Although none are definitive, these studies are provocative in potentially relating the apparent increase in aldosteronism to concurrent increases in obesity.

## **Evaluation and Diagnosis of Primary Aldosteronism**

Patients in whom screening for PA is recommended include the following: (1) patients presenting with hypokalemia, including in the setting of ongoing thiazide diuretic use; (2) patients with resistant hypertension; (3) patients with a history of severe hypertension; (4) patients at risk of having a secondary cause of hypertension such as early onset of high BP, abrupt worsening of hypertension, or abrupt loss of BP control in a patient who had been easily controlled previously; and (5) patients found to have an incidental adrenal mass.

PA can be reliably screened for by measurement of the ARR.<sup>47</sup> The ARR should be measured in the early morning in ambulatory patients. Hypokalemia should be corrected for at least 4 weeks before measurement as low serum potassium levels will suppress aldosterone release. Aldosterone antagonists (spironolactone, eplerenone) will falsely increase plasma aldosterone levels and must be withdrawn for 4-6 weeks before testing. Potassium-sparing diuretics such as amiloride and triamterene can stimulate aldosterone release if they have significantly increased serum potassium levels and so should also be withdrawn if possible.

Ideally all antihypertensive medications should be withdrawn before measurement as the various agents may increase (ACEIs, ARBs, diuretics) or

decrease (beta-blockers) PRA. However, even if the ARR is measured during ongoing treatment, the ARR still has a high sensitivity and therefore is an effective screening test. If a high ratio is observed during ACEI, ARB, and/or diuretic use, it is even more suspicious for aldosterone excess as the effect of the medications would be to lower the ratio.

The ARR is generally considered positive if elevated above 20 (with plasma aldosterone measured in ng/dL and the PRA in ng/mL/h). The ratio is, however, highly denominator dependent, such that an extremely low PRA can result in a falsely high ratio. This risk can be avoided by using a minimum PRA of 0.5 mg/mL/h to calculate the ratio, or alternatively, requiring a minimum plasma aldosterone of >12 ng/dL for the ARR to be considered high.

While the ARR has a high negative-predictive value (a low value reliably excludes PA), it has a low positive-predictive value. That is, many patients with a high ratio will be excluded from having PA upon confirmatory testing. This undoubtedly reflects the high prevalence of “low-renin” hypertension, particularly in patients with resistant hypertension. An increasingly high ARR (>50) more likely represents true PA, but suppression testing should still be done to confirm the diagnosis (Fig 5).

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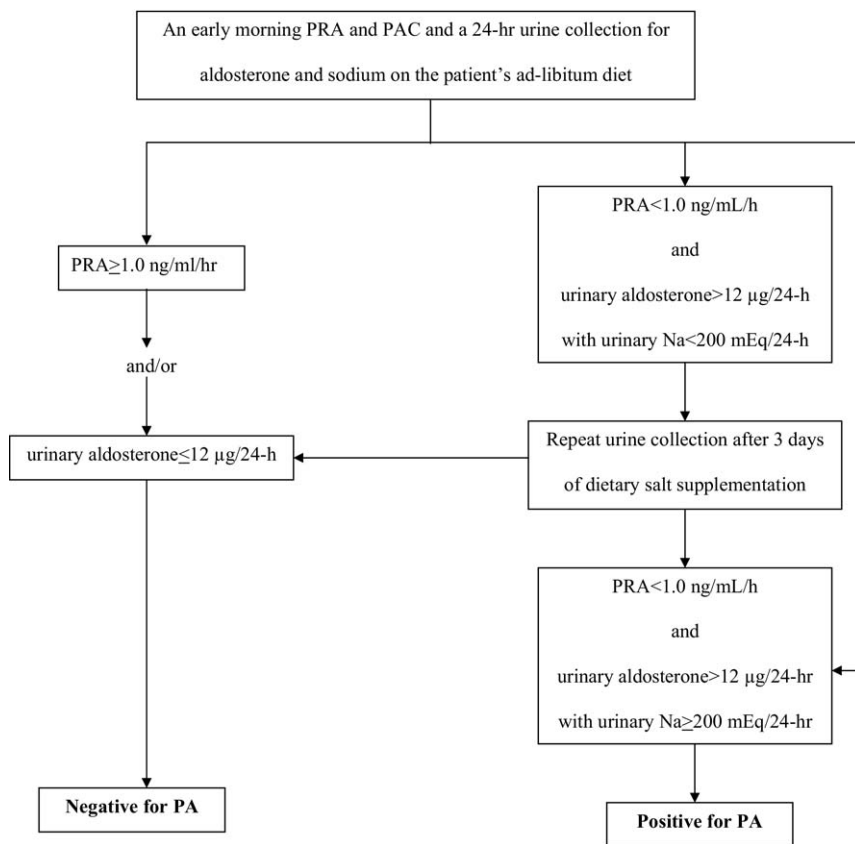
**Jay Cohn:** Is documentation of excess circulating aldosterone really necessary? If the syndrome is so common and the treatment with an aldosterone inhibitor so effective, why not merely initiate therapy? After all, trial and error has become the standard approach to selecting antihypertensive therapy.

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## *Confirmatory Testing*

Confirmation of PA requires demonstration of failure to suppress high aldosterone levels with inhibition of renin activity either with volume expansion or with pharmacologic blockade of the renin-angiotensin pathway. The gold standard historically has been volume expansion with fludrocortisone administration and concomitant high dietary salt intake. With fludrocortisone suppression testing, fludrocortisone 0.1 mg is administered orally every 6 hours for 4 days during high dietary salt intake ( $\geq 12$  g daily). Failure to suppress the morning upright plasma aldosterone level to <6 ng/dL is considered positive for PA. Fludrocortisone suppression testing can result in severe increases in BP and/or profound decreases in serum potassium levels such that hospitalization during testing is necessary for close monitoring and treatment of





**FIG 5.** Flow chart for the diagnostic evaluation for primary aldosteronism. PRA, plasma renin activity; PAC, plasma aldosterone concentration; Na, sodium. (Adapted with permission from Nishizaka MK, Pratt-Ubunama M, Zaman MA, et al. Validity of plasma aldosterone-to-renin activity ratio in African American and white subjects with resistant hypertension. *Am J Hypertens* 2005;8:805-12).

hypertension and hypokalemia as necessary. This need for hospitalization limits the practicality of the fludrocortisone testing.

More practical than the fludrocortisone suppression testing is dietary salt loading as an outpatient. In addition to their normal diet patients are advised to take NaCl tablets (4-6 g divided between meals) for 4 days. On the fourth day of salt loading, patients collect a 24-hour urine. Failure to suppress urinary aldosterone to <12-14  $\mu\text{g}/24$  hours during high sodium intake (>200 meq/24 hours) confirms the diagnosis of PA. Such dietary salt loading is generally safe and well tolerated. Patients may experience some nausea, which can be minimized by ingesting the supplemental salt

with meals or snacks. Severe elevations in BP are unusual but patients should be advised to monitor their BP and discontinue the salt loading if the BP increases markedly. Risk of severe increases in BP is elevated in patients with chronic kidney disease and in the elderly and so salt loading should be done cautiously in such patients. Salt loading should not be done in patients with a history of congestive heart failure. Many patients are chronically ingesting a high salt diet such that their sodium excretion normally exceeds 200 meq/24 h. Accordingly, it is reasonable to first check aldosterone and sodium excretion during the subject's normal diet and, if the sodium is high, additional salt loading is not necessary to interpret the aldosterone excretion. Such an approach is recommended in evaluating patients whose BP remains poorly controlled.

Salt loading can also be accomplished with intravenous infusion of 2 L of normal saline over 4 hours. Failure to suppress plasma aldosterone to <10 ng/dL is positive for PA. Saline infusion testing should be done in the morning to avoid falsely negative results secondary to circadian-related decreases in aldosterone levels.

The captopril suppression test is performed by measuring plasma aldosterone before and 2 hours after oral administration of captopril 25 mg. The test is considered positive for PA if the plasma aldosterone fails to suppress <15 ng/dL. Patients must have been withdrawn from ACEIs and/or ARBs for 2-4 weeks before conducting the test. The sensitivity and specificity of the captopril test has been favorably compared to salt loading in a small number of studies but more widespread validation is needed. It is a reasonable alternative when salt loading is not possible.

### *Subtype Determination*

Historically, PA was thought to be most often idiopathic in etiology presumably secondary to bilateral adrenal hyperplasia and with a minority of patients having an aldosterone producing adenoma. Differentiation of subtype is clinically relevant as unilateral aldosterone-producing adenomas can be surgically removed by adrenalectomy, while PA secondary to bilateral hyperplasia will not benefit from surgery. Recent studies indicate, however, that more than 40% of patients with PA may have the disease secondary to an aldosterone-producing adenoma,<sup>48</sup> such that cure of the disease with adrenalectomy may be possible in a larger proportion of PA patients than thought previously.

Patients confirmed with PA should undergo thin-cut (2-3 mm) computed tomography imaging of the adrenal glands. Computed tomography imaging, however, has a poor sensitivity and specificity in terms of identifying adrenal adenomas. Studies suggest that the concordance

between computed tomography imaging and adrenal vein sampling is only about 40%,<sup>49</sup> such that if the results of computed tomography scanning alone are used to guide therapy, inappropriate treatment (medical vs. surgical) may be decided upon in up to one-half of the patients with PA. Computed tomography imaging, however, is still recommended as part of the evaluation for PA in order to (1) visually localize tumors prior to adrenal vein sampling; (2) identify particularly large tumors (>3-4 cm) that may warrant resection because of increased risk of cancer; and (3) visualize the local anatomy prior to adrenal vein sampling and/or adrenalectomy, including potentially localizing the origin of the adrenal veins. If a tumor is not seen on computed tomography imaging, medical therapy is more likely appropriate, recognizing, however, that the patient may still have an aldosterone-producing microadenoma below the resolution of the computed tomography scanning. An aldosterone-producing adenoma is suggested by more severe hypertension, a history of hypokalemia, and higher aldosterone levels, but there is enough overlap in these characteristics in PA patients with and without aldosterone-producing adenomas that adrenal vein sampling is needed to confirm lateralization of aldosterone secretion before recommending adrenalectomy.

Patients with confirmed PA will potentially benefit from adrenalectomy if there is lateralization of aldosterone secretion secondary to a unilateral aldosterone-producing adenoma or unilateral hyperplasia (the latter being a very rare cause of PA). Patients with bilateral hyperplasia or bilateral aldosterone-producing adenomas are unlikely to benefit from surgery. Accordingly, all PA patients for whom adrenalectomy is being considered should undergo adrenal vein sampling to confirm lateralization of aldosterone secretion. Adrenal vein sampling is a technically difficult procedure, particularly in terms of successfully cannulating the right adrenal vein. Even with experience, success rates for obtaining samples from both adrenal veins are around 80%. Patients should therefore be referred to institutions experienced in doing the procedure and in interpreting the results. The procedure should be performed after withdrawal of medications that may affect aldosterone secretion. This specifically includes spironolactone and eplerenone, and ideally, other potassium-sparing diuretics, ACEIs, and ARBs.

## **Treatment of Primary Aldosteronism**

### *Adrenalectomy*

Patients with an aldosterone-producing adenoma will likely benefit from adrenalectomy. The procedure should be done laparoscopically to

minimize postoperative recovery time. Hypokalemia is almost always corrected with removal an aldosterone-producing adenoma. While the BP generally improves with adrenalectomy, the majority of patients will still need some antihypertensive treatment. Younger patients, patients with less severe hypertension, and patients who responded favorably to spironolactone are more likely to manifest the largest BP benefit, including in some cases, total cure of their hypertension.

Postoperatively, aldosterone secretion from the contralateral adrenal gland may be suppressed. Accordingly, a high salt diet should be recommended in the initial postoperative period and the serum potassium levels should be monitored weekly for about 4 weeks as hyperkalemia, although rare, can occur. The BP medications should be down-titrated or discontinued depending upon the initial BP response. The BP should be monitored closely in the postoperative period with further adjustments made to the antihypertensive regimen as needed.

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**Jay Cohn:** Is there any evidence that long-term outcome is improved by surgery as opposed to medical therapy? It seems that such a study would be mandatory before advocating diagnostic efforts and surgical intervention. Given the prevalence of the disease reported by the authors, such a study could be undertaken.

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## *Pharmacologic Therapy*

Patients with idiopathic PA, patients with bilateral adenomas, or patients in whom adrenalectomy is not being considered should be treated with mineralocorticoid antagonists. Spironolactone, a nonselective aldosterone antagonist, is the conventional agent for treating PA. It is typically dosed 25-200 mg daily, with titrations being done at 4-6 weeks. If the patient has been receiving potassium supplementation, it should be discontinued upon starting spironolactone. If exceptionally large doses of potassium were needed, it may be appropriate to significantly down-titrate the potassium dose with subsequent discontinuation as the spironolactone is up-titrated. In some patients, however, both spironolactone use and potassium supplementation may be needed to prevent hypokalemia.

Particularly in older patients, spironolactone alone may not be sufficient to control BP. All other classes of antihypertensive agents can be used in combination with spironolactone, although use of a thiazide diuretic will maximize BP benefit while reducing risk of hyperkalemia. ACEIs and ARBs increase risk of hyperkalemia if used with spironolactone. Non-steroidal anti-inflammatory drugs also increase risk of hyperkalemia. In

general, risk of hyperkalemia is increased in patients with chronic kidney disease, including the elderly and patients with diabetes. The serum potassium level should be monitored approximately 4 weeks after initiating or titrating spironolactone. In patients at risk of hyperkalemia or in patients at risk of hypokalemia because of discontinuation or down-titration of large doses of potassium supplements, the serum potassium should be checked as early as 1 week after starting spironolactone. Patients receiving spironolactone should be advised against ingestion of over-the-counter compounds that may contain potassium such as salt substitutes or herbal preparations. Acute declines in renal function can occur with spironolactone use, but it usually occurs in conjunction with large reductions in BP, such that withdrawal or down-titration of the spironolactone is often sufficient to return blood urea nitrogen and creatinine to baseline levels.

Spironolactone is generally well tolerated. The most common adverse effect is breast tenderness with or without gynecomastia. The occurrence of breast tenderness is uncommon with low doses of spironolactone, but the incidence increases sharply as doses exceed 50 mg daily. Other adverse effects include erectile dysfunction and menstrual irregularities. These effects may be delayed in occurring for up to a year.

Eplerenone is a selective mineralocorticoid receptor antagonist with much less cross-reactivity with androgen and progesterone receptors such that sex-related adverse effects are uncommon. It has been shown to be an effective antihypertensive agent in treating general hypertension and low-renin hypertension; however, its efficacy has not been established in treating PA. If spironolactone is not tolerated, eplerenone is a reasonable alternative. Eplerenone is not as potent as spironolactone and so switching from the latter to the former will likely require higher doses to achieve the same benefit. The recommended dose range of eplerenone for general hypertension is 50-100 mg daily.

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**Jay Cohn:** The relationship between aldosterone and morbidity and mortality in heart failure is not so simple. In a large study of over 4000 patients, measurement of a panel of circulating hormone levels demonstrated that aldosterone levels were not independently predictive of outcome (Latini R, Masson S, Anand I, et al, for the Val-HeFT Investigators. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004;25:292-9). In contrast norepinephrine is a powerful predictor (Latini R, Masson S, Anand I, et al, for the Val-HeFT Investigators. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004;25:292-9; Cohn JN, Levine TB, Olivari MT, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive

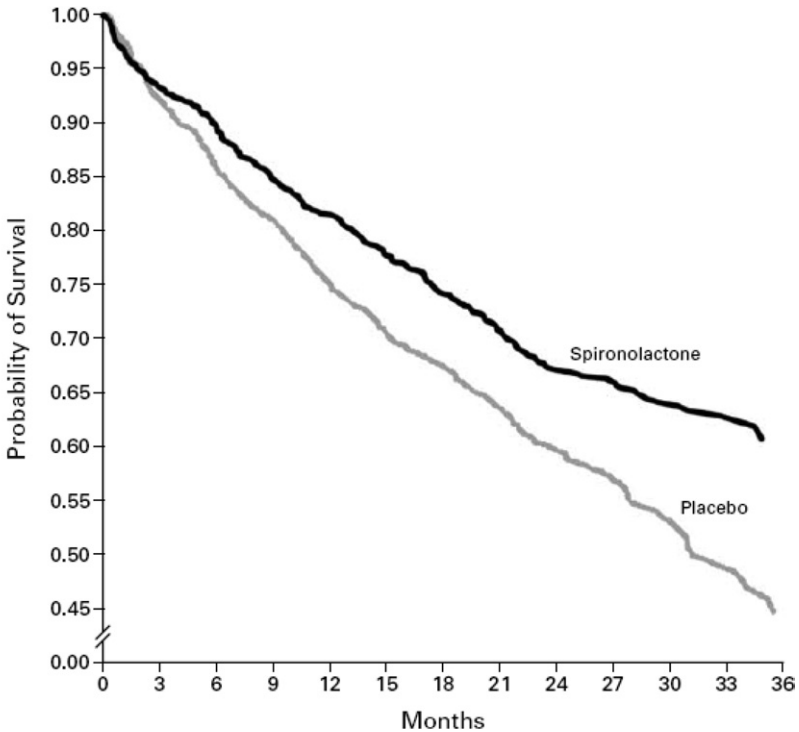
heart failure. *New Engl J Med* 1984;311:819-23). Nonetheless, reducing norepinephrine levels does not improve outcome (Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003;5:659-67), whereas blocking aldosterone does. Clearly we have much left to learn.

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## Aldosterone and Congestive Heart Failure

In the early ACEI trials of congestive heart failure, plasma aldosterone was shown to predict subsequent morbidity and mortality, suggesting a contributory role of aldosterone in the progression of established systolic dysfunction.<sup>50</sup> Based in part on this observation, the Randomized Aldactone Evaluation Study (RALES) was initiated to evaluate the benefit of adding mineralocorticoid receptor antagonism to conventional treatment.<sup>51</sup> This study was performed in 1663 patients with New York Heart Association class III or IV heart failure with an ejection fraction of 35% or less and while being treated with an ACEI and a loop diuretic. Patients were randomly assigned in a double-blind fashion to receive either spironolactone 25-50 mg or matching placebo. After approximately 2 years of follow-up, spironolactone decreased mortality by 30% (Fig 6) and hospitalizations for congestive heart failure exacerbations by 35%. The reduction in death in the spironolactone arm was attributed to a lower risk of death from progressive heart failure and sudden death. The results were significant in demonstrating benefit of mineralocorticoid receptor blockade beyond renin-angiotensin inhibition in patients with chronic systolic dysfunction.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), benefit of adding eplerenone to standard of care for treatment of heart failure following acute myocardial infarction was tested.<sup>52</sup> Over 6600 patients with left ventricular ejection fraction of 40% and or less, 3 to 14 days after an acute myocardial infarction, were randomized to eplerenone 25-50 mg daily or placebo in addition to conventional medical therapy with an ACEI or ARB, diuretics, beta-blockers, as well as coronary reperfusion therapy as appropriate. Treatment with eplerenone reduced all-cause mortality by 15% and cardiovascular death or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia by 13%. These findings extended the results of the RALES study in implicating aldosterone as an important mediator of cardiovascular risk following myocardial function complicated by impairment of systolic function. Neither



No. AT Risk

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

**FIG 6.** Kaplan–Meier analysis of the probability of survival among patients in the placebo group and patients in the spironolactone group in the Randomized Aldactone Evaluation Study (RALES) study. The risk of death was 30% lower among patients in the spironolactone group than among patients in the placebo group ( $P < 0.001$ ). (Reprinted with permission from Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.)

RALES nor EPHEsus was designed to determine mechanisms underlying benefit with mineralocorticoid receptor blockade.

Proposed effects include more effective diuresis and associated reduction in filling pressures, an antiarrhythmic effect secondary to minimizing unfavorable shifts in intracellular potassium levels, and/or blunting the thrombogenic effects of aldosterone.

As with treating hypertension, caution must be exercised in using spironolactone or eplerenone for treatment of congestive heart failure because of risk of severe hyperkalemia. A recent analysis done in Canada

suggests since the publication of RALES there has been an increased number of hospitalizations for and death from hyperkalemia in patients with congestive heart failure.<sup>53</sup> Risk of hyperkalemia is increased in patients with congestive heart failure because of concomitant use of ACEIs and/or ARBs, underlying kidney disease, renal hypoperfusion secondary to poor cardiac output and/or diuresis, and common use of other pharmacologic agents predisposing to hyperkalemia, such as non-steroidal anti-inflammatory agents. When initiating and titrating spironolactone or eplerenone in patients with heart failure, renal function and serum potassium levels must be monitored closely, particularly in patients with underlying chronic kidney disease and/or in patients on high doses of loop diuretics.

## **Aldosterone and Heart Disease**

While aldosterone is predictive of and use of mineralocorticoid receptor antagonists improves survival in patients with chronic congestive heart failure, data are beginning to emerge linking aldosterone to ischemic heart disease separate from congestive heart failure. In a recently published evaluation, Beygui et al reported that plasma aldosterone levels drawn soon after hospital admission predicted cardiovascular morbidity and mortality in patients who had presented with acute ST segment elevation myocardial infarction.<sup>54</sup> Patients in the highest quartile of plasma aldosterone level had a more than 2-fold increase in 6-month mortality compared to patients with lower aldosterone levels as well as significantly more postinfarction cardiovascular complications including ventricular fibrillation, resuscitated cardiac arrest, and new or worsening congestive heart failure. Multivariate analysis indicated that the risk imparted by higher aldosterone levels was independent of other major prognostic indicators. Although ejection fractions were not reported, the large majority of patients upon presentation did not have clinical evidence of congestive heart failure.

This study is clinically important in suggesting that high aldosterone levels negatively impact cardiovascular outcomes following myocardial infarction even in patients with preserved systolic function. In the EPHEBUS trial, patients presenting with acute myocardial infarction complicated by systolic dysfunction benefited from receiving eplerenone within 3-14 days of admission. The results of Beygui et al extend those results in suggesting that the unfavorable effects of aldosterone in the setting of acute myocardial infarction are not limited to congestive heart failure and may include a broader array of cardiovascular complications including, in particular, fatal arrhythmias.



## Aldosterone and Kidney Disease

Experimental studies have demonstrated the independent role of aldosterone in causing renal injury. As discussed earlier, multiple investigators have reported that rats infused chronically with aldosterone and maintained on a high salt diet develop perivascular inflammation and then progressive fibrosis in target organs, including the kidney.<sup>15-18,55</sup> Studies demonstrating protection of renal function with use of mineralocorticoid receptor antagonists even in the absence of demonstrable aldosterone excess lends further support to the role of aldosterone in contributing importantly to renal decline. Rocha et al implanted time-release pellets of spironolactone in saline-drinking stroke-prone spontaneously hypertensive rats, a model of severe hypertension that is not thought to be aldosterone dependent.<sup>55</sup> The spironolactone-treated animals developed less proteinuria and had increased survival compared to the control group despite similar systolic BP levels. Microscopic examination of the kidneys and brain revealed a marked protective effect of spironolactone against the development of malignant nephrosclerotic and cerebrovascular lesions. These findings demonstrated the protective effect of spironolactone and an important role for mineralocorticoids as hormonal mediators of vascular injury even in seemingly normal or low aldosterone models of hypertension.

As in animal studies, elevated levels of aldosterone are associated with renal injury in humans. A decade after they described the index case of a patient with an aldosterone-secreting adrenal tumor, Conn et al found that 85% of patients with PA also had proteinuria.<sup>56</sup> Proteinuria is an early sign of nephropathy associated with progressive glomerulosclerosis, tubulointerstitial inflammation, and scarring, and often leading to progressive loss of renal function in both diabetic and nondiabetic subjects. This is clinically relevant to the current discussion as proteinuria is a strong independent predictor of increased cardiovascular risk.<sup>57,58</sup>

Several observational studies have shown that patients with PA have higher levels of urinary protein excretion compared to patients with primary hypertension.<sup>59-63</sup> In a large cross-sectional analysis of mostly normotensive 2700 participants, Framingham investigators related albuminuria to plasma aldosterone levels.<sup>59</sup> The authors showed that the highest quintile of aldosterone levels was associated with a 21% higher level of urinary albumin excretion compared to the lowest quintile. Overall a positive but nonlinear relation with serum aldosterone was observed between the degree of albuminuria and aldosterone levels. This nonlinear relation may have been secondary to the low prevalence of

hyperaldosteronism in normotensive persons or possibly due to a threshold effect of relating aldosterone in causing target-organ damage, that is, the untoward effects of aldosterone may not manifest until the aldosterone is in physiologic excess.

The PA Prevalence in Hypertensives study prospectively determined urinary albumin excretion in 490 hypertensive patients, 64 of whom were confirmed to have PA.<sup>60</sup> Patients with PA, regardless of whether secondary to an aldosterone-producing adenoma or presumed idiopathic hyperaldosteronism, had higher 24-hour urinary albumin excretion rates than the subjects with primary hypertension, despite similar BP levels. This suggests that hyperaldosteronism accelerates renal decline beyond that attributable to the associated elevated BP.

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**Jay Cohn:** Since endothelial dysfunction is associated with microvascular renal abnormalities that induce microalbuminuria, the endothelial dysfunction induced by aldosterone may be an important culprit.

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Aldosterone-induced proteinuria excess is likely related, at least in part, to intravascular fluid expansion and consequent increases in glomerular filtration rate (ie, hyperfiltration). Sechi et al prospectively compared the renal function of 50 patients with PA to subjects with primary hypertension matched for age, gender, body mass index, and estimated duration of hypertension.<sup>62</sup> Patients with PA were followed for 6.4 years after treatment with adrenalectomy or mineralocorticoid receptor antagonist. Despite similar BP reduction, the decreases in glomerular filtration rate and albuminuria were significantly greater in the PA group, suggesting to the authors that aldosterone-induced proteinuria in humans is related to intravascular volume retention and subsequent increases in glomerular filtration rate. Such an effect does not exclude a direct toxic effect of aldosterone on glomerular structure separate from the hyperfiltration effects.

Unlike the animal models of hyperaldosteronism and high dietary salt, an interaction between aldosterone and dietary salt in modulating organ-target damage has not been observed. Framingham investigators in their mostly normotensive cohort demonstrated that high dietary salt was positively related to urinary albumin excretion but did not find that high plasma aldosterone levels combined with high urinary sodium excretion was associated with worse albuminuria.<sup>59</sup> However, few studies have assessed the potential interaction between endogenous aldosterone and various levels of dietary salt intake, particularly in hypertensive cohorts.<sup>64</sup>

Despite the absence of randomized placebo-controlled trials, treatment with either adrenalectomy or aldosterone receptor blocker seems to lessen proteinuria in patients with PA. Ribstein et al reported higher urinary excretion of protein in 25 patients with PA compared to control subjects with primary hypertension.<sup>63</sup> In this study, PA subjects were followed for 6 months after adrenalectomy or spironolactone treatment. There was a significant decrease in proteinuria with treatment of the aldosterone excess with either modality.

Additional evidence demonstrates the benefits of mineralocorticoid receptor antagonists in reducing albuminuria in patients with chronic kidney disease or diabetic nephropathy.<sup>65-68</sup> In a randomized, double-blind study the antiproteinuric effect of spironolactone 25-50 mg daily on top of chronic treatment with an ACEI or an ARB was compared to placebo in patients with nephropathy secondary to type 2 diabetes.<sup>66</sup> In this study, albuminuria decreased by 40% in the 29 patients treated with spironolactone compared to the 30 placebo-treated patients. In a separate study, significant antiproteinuric benefit of spironolactone was observed in type 1 diabetics with microalbuminuria.<sup>67</sup> Last, Epstein et al have reported suppression of albuminuria with eplerenone in patients with type 2 diabetes.<sup>68</sup> Eplerenone in doses of 50 mg and 100 mg when added to baseline ACEI therapy markedly reduced the urinary albumin:creatinine ratio in comparison with placebo. In this study, the antiproteinuric benefit was similar with either dose of eplerenone.

The efficacy of mineralocorticoid receptor antagonism in abrogating proteinuria beyond that of an ACEI or ARB likely reflects incomplete blockade of renin-angiotensin and subsequent aldosterone escape with use of these latter medications. To what degree the additional reduction in proteinuria achieved with mineralocorticoid receptor antagonists is related to better diuresis and/or BP control needs to be determined.

## **Aldosterone and the Metabolic Syndrome**

The metabolic syndrome is characterized by a constellation of cardiovascular risk factors including abdominal obesity, dyslipidemia (elevated triglycerides and lower HDL-cholesterol concentrations), elevated BP, and insulin resistance with or without glucose intolerance. It is thought to represent a prothrombotic and a proinflammatory state.<sup>69</sup> Recent observations suggest that aldosterone is associated with the metabolic syndrome and/or its separate components.<sup>70-73</sup> In a family-based study of 356 participants from 69 families of African descent aimed at examining genetic determinants of hypertension,<sup>70</sup> plasma aldosterone levels were significantly higher in participants with than without the metabolic

syndrome. In multivariable models, plasma aldosterone was significantly associated with all components of the metabolic syndrome except for fasting blood glucose. In contrast, PRA was positively associated only with triglycerides and fasting blood glucose levels. Plasma aldosterone, but not renin activity, was associated with the metabolic syndrome per se independent of the association with its separate components.

This association between aldosterone levels and risk of having the metabolic syndrome has been observed in other studies including one by Kidambi et al.<sup>71</sup> In this study of 397 African Americans in Milwaukee, the investigators found that hypertensive compared to normotensive subjects had greater waist circumference and unfavorable lipid profiles, were more insulin resistant, and had lower renin activity and higher plasma aldosterone and both late-night and early-morning salivary cortisol concentrations. Ambulatory BP was positively correlated with plasma aldosterone and late-night salivary cortisol and inversely correlated with renin activity. Plasma aldosterone correlated significantly with waist circumference, total cholesterol, triglycerides, insulin, and the insulin-resistance index. Based on Adult Treatment Panel III criteria, 17% of all of the subjects were classified as having the metabolic syndrome. Plasma aldosterone levels, but not renin activity, were elevated in subjects with the metabolic syndrome.

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**Jay Cohn:** This admonition is appropriate and important, not only for the metabolic syndrome but also for the other disease states discussed. Prospective clinical trials are urgently needed.

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Similarly, investigators in Italy have demonstrated that the prevalence of the metabolic syndrome is higher in hypertensive patients with PA than in patients with presumed primary hypertension.<sup>72</sup> In a separate study, these investigators also found that plasma adiponectin levels and insulin sensitivity were lower in patients with PA compared to patients with low renin hypertension.<sup>73</sup>

These multiple cross-sectional studies strongly link higher aldosterone levels to the risk of having the metabolic syndrome and/or several of its components. To confirm causality, what is needed are prospective studies demonstrating that aldosterone studies predict development of the metabolic syndrome as has been observed with development of hypertension, or separately, intervention studies with mineralocorticoid receptor antagonists demonstrating reversal or at least improvement in the various components of the metabolic syndrome. Until such evidence is available,

the associations between aldosterone and the metabolic syndrome are provocative but aldosterone excess as cause of the metabolic syndrome cannot be presumed.

## **Cardiovascular Disease in Patients with Primary Aldosteronism**

Given the strong associations demonstrated between aldosterone and the separate cardiovascular disease processes including hypertension, coronary heart disease, chronic kidney disease, and congestive heart failure, one would anticipate that patients with chronic aldosterone excess, ie, classical PA, would manifest a considerably higher rate of cardiovascular complications than patients with primary hypertension. Observational studies have suggested this to be the case. Although it is difficult to reliably match patients for both the duration and the severity of hypertension, comparisons of patients with PA and primary hypertension suggest that the former are more likely to have suffered cardiovascular complications. In one such report, patients diagnosed with PA were more than four times as likely to have had a stroke, 6.5 times as likely to have had a myocardial infarction, and more than 12 times as likely to have developed atrial fibrillation compared to general hypertensive patients matched as much as possible for duration and severity of hypertension.<sup>74</sup> Such a wide disparity in the rate of cardiovascular complications is consistent, although hardly confirmatory, of aldosterone contributing broadly to development and/or progression of cardiovascular disease.

## **Conclusion**

Observational data strongly link aldosterone levels to risk of multiple cardiovascular disease processes including hypertension, congestive heart failure, coronary heart disease, chronic kidney disease, and the metabolic syndrome. For hypertension, congestive heart failure, and chronic kidney disease, interventional studies with mineralocorticoid receptor antagonists confirm aldosterone as an important underlying contributor to the respective disease entity as demonstrated, respectively, by significant reductions in BP, mortality, and proteinuria. Much of the benefit of mineralocorticoid receptor antagonists in each of these situations seems to be from better naturesis and diuresis with subsequent reductions in intravascular volume, intracardiac volumes, and glomerular filtration rate. Animal studies suggest a direct toxic effect of aldosterone in promoting inflammation and fibrosis separate from BP and fluid retention. Reversal or suppression of these effects undoubtedly contributes to the broad cardio-

vascular benefit of mineralocorticoid receptor antagonists, but to what degree has not been established. Last, prospective studies indicate that high plasma aldosterone levels strongly predict worsening of BP and development of incident hypertension. This raises the possibility of better preventing hypertension with early use of mineralocorticoid receptor antagonists in at-risk subjects. One can speculate based on the observational data similar benefit in terms of reversing or slowing development of the metabolic syndrome. Long-term, well-conducted studies will be needed, but demonstration of such preventive benefit would confirm aldosterone as an important mediator of long-term cardiovascular risk.

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**Jay Cohn:** The authors have provided a comprehensive review of a potentially important and under-appreciated mechanism of hypertension and vascular damage. If the authors are right, we have been dramatically under-recognizing and mistreating inappropriate levels of aldosterone in patients with hypertension and other vascular diseases. The clinical availability of an inexpensive, generic aldosterone inhibitor has discouraged industry support of clinical trials to document efficacy of the therapy. Other sources of support should be made available to carry out the kind of prospective outcome and mechanistic trials necessary to identify the proper place in management for aldosterone inhibition.

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