A growing body of evidence links aldosterone excess to the development and progression of several different cardiovascular disease processes, including hypertension, congestive heart failure, chronic kidney disease, coronary artery disease, and stroke. The association with aldosterone is particularly strong for hypertension, with multiple studies independently suggesting that aldosterone contributes broadly to the development and severity of hypertension separate from the presence of classically defined primary aldosteronism (PA). In these same studies, renin activity, if measured, has not been related to blood pressure levels, which suggests an autonomous role of aldosterone in causing hypertension separate from renin–angiotensin II.

Prospective and cross-sectional studies suggest that aldosterone contributes both to the development and the severity of hypertension. In a recent prospective analysis done as part of the ongoing Framingham Offspring Study, serum plasma aldosterone levels in normotensive subjects predicted subsequent increases in blood pressure and in the development of incident hypertension. During a 4-year follow-up, subjects in the highest quartile of serum aldosterone level, relative to subjects in the lowest quartile, had a 1.60-fold higher risk of significantly increased blood pressure and a 1.61-fold higher risk of hypertension.

Cross-sectional studies demonstrate a significant correlation between plasma aldosterone levels and untreated 24-hour ambulatory blood pressure levels. In an evaluation of black American and white French Canadian subjects, supine and standing plasma aldosterone levels were significantly related to daytime and nighttime systolic and diastolic blood pressure levels in the black American subjects. In the white Canadian subjects, standing aldosterone levels correlated with both daytime and nighttime diastolic blood pressure. In both ethnic groups, blood pressure levels were unrelated to plasma renin activity, suggesting that aldosterone, more so than renin–angiotensin II, contributed to the severity of hypertension.

Aldosterone excess as indicated by the presence of classic PA is surprisingly common in hypertensive patients, particularly in patients with resistant hypertension. Historically, PA was reported to be an uncommon cause of hypertension, with a prevalence of <1% among general hypertensive patients. Beginning in the early 1990s, however, with reports from investigators in Brisbane, Australia, the prevalence of PA has been found to be considerably higher, occurring in perhaps 5% to 10% of hypertensive patients. In a particularly compelling study, more than 600 patients with hypertension were evaluated for PA, first by screening of the plasma aldosterone/plasma renin activity ratio, and then, if indicated, confirmation with fludrocortisone-suppression testing. At some point before the biochemical investigation, patients had been withdrawn from antihypertensive treatment, such that the investigators were able to relate the severity of the untreated hypertension to the presence of PA. The overall prevalence of PA was 6.1%. However, the risk of PA increased with increasing severity of hypertension, such that PA was uncommon (<2%) in subjects with mild hypertension (<160/100 mm Hg) but present in 8% of patients with moderate hypertension (160 to 179/100 to 109 mm Hg) and in 13% of patients with severe hypertension (>180/110 mm Hg). This and multiple other studies suggest that PA is a much more common cause of hypertension than previously described and that the incidence of PA increases with increasing severity of hypertension.

PA is particularly common in patients with resistant hypertension. In an evaluation conducted at the University of Alabama at Birmingham, PA was diagnosed in 20% of consecutive patients referred for resistant hypertension. A similarly high occurrence of PA in patients with resistant or poorly controlled hypertension was observed in separate investigations by investigators in Seattle, Wash; Oslo, Norway; and Prague, Czech Republic, suggesting that aldosterone excess commonly underlies resistance to antihypertensive treatment.

Beyond hypertension, an increasing number of studies link aldosterone excess to other cardiovascular disease processes. In congestive heart failure, higher plasma aldosterone and angiotensin II levels predict increased mortality. Cross-sectional studies implicate aldosterone excess as a probable contributor to the development of chronic kidney disease. In an evaluation of 2700 participants in the Framingham Cohort Study, urinary sodium excretion was a strong positive predictor of urinary albumin excretion. In addition, the top quintile of serum aldosterone levels were associated with a 21% higher urinary albumin excretion than the lowest quintile. In a separate study, patients with confirmed PA had significantly higher urinary albumin excretion compared with subjects with primary hypertension. Other clinical studies have shown that chronic aldosterone excess is associated with
increased left ventricular hypertrophy, greater diastolic dysfunction, exacerbation of endothelial dysfunction, and, recently, increased risk of various components of the metabolic syndrome.12

Consistent with these negative effects on cardiovascular risk factors, observational studies suggest that PA is associated with a rate of cardiovascular complications that seems to exceed that of primary hypertension. In one such comparison, patients diagnosed with PA were more than 4 times as likely to have had a stroke, 6.5 times as likely to have had a myocardial infarction (MI) and more than 12 times as likely to have developed atrial fibrillation than general hypertensive patients matched as much as possible for duration and severity of hypertension.13

Although observational studies have generated much smoke suggesting that aldosterone contributes importantly to the development of cardiovascular disease, they do not prove causality. However, a smaller number of interventional studies with aldosterone antagonists confirm that there is fire underlying this smoke. In hypertension, studies of eplerenone, a selective mineralocorticoid receptor antagonist, have shown antihypertensive benefit comparable with that of other classes of agents, with particular benefit in patients with low-renin hypertension.14 In patients with resistant hypertension, spironolactone, when added to existing multidrug regimens, has provided antihypertensive benefit (>20/10 mm Hg) to a degree exceeding what would be anticipated with other classes of agents.15 Aldosterone antagonists, even when added to renin–angiotensin blockers, reduce proteinuria in patients with chronic kidney disease.16 In heart failure, the Randomized Aldactone Evaluation Study (RALES) indicated that addition of low-dose spironolactone to regimens that included (in most patients) an angiotensin-converting enzyme inhibitor significantly improved survival by 30%.17 In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, eplerenone added to an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker and beta blocker improved survival by 15% in patients with left ventricular dysfunction after acute MI.18 In showing benefit by directly blocking the mineralocorticoid receptor, these intervention studies support the role of aldosterone in directly contributing to development and/or progression of cardiorenal disease.

**Aldosterone and Cardiovascular Complications After MI**

In the current edition of *Circulation*, Beygui and colleagues19 extend data linking aldosterone to cardiovascular risk, finding that plasma aldosterone levels drawn soon after admission predict cardiovascular morbidity and mortality in patients presenting with acute ST-segment elevation MI. Patients in the highest quartile of plasma aldosterone level had a more than 2-fold increase in 6-month mortality compared with patients with lower aldosterone levels; patients in the highest quartile also had significantly more post-MI cardiovascular complications, such as 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 are not reported, the large majority of patients did not have clinical evidence of congestive heart failure on presentation, with 83% being Killip class 1.

This study is clinically important because it suggests that high aldosterone levels negatively impact cardiovascular outcomes after MI, even in patients with preserved systolic function. In the EPHESUS trial, patients presenting with acute MI complicated by systolic dysfunction benefited from receiving eplerenone within 3 to 14 days of admission. The current results are novel in suggesting that the unfavorable effects of aldosterone in the setting of acute MI are not limited to congestive heart failure and may include a broader array of cardiovascular complications, including fatal arrhythmias.

The current study is observational, and therefore, mechanisms by which aldosterone may worsen cardiovascular complications cannot be inferred. A large body of experimental evidence has demonstrated that aldosterone excess in combination with high dietary salt intake induces perivascular inflammation and fibrosis.20 These effects occur in multiple organs including the heart, kidney, and brain. In addition, human studies suggest a variety of other effects presumed to negatively affect cardiovascular risk, such as suppression of nitric oxide activity, impairment of endothelial function, and stimulation of thrombogenic pathways.21

With these effects in mind, one can speculate that aldosterone excess may have contributed in the short term and/or the long term to worse outcomes after acute MI. In the short term, patients with greater aldosterone release in response to an MI may have suffered from inappropriate fluid retention, proarrhythmic effects secondary to unfavorable shifts in intracellular potassium or magnesium levels, and/or increased thrombogenesis. Alternatively, the higher aldosterone levels measured on hospitalization may have reflected chronically increased aldosterone levels preceding the MI. If so, chronic aldosterone excess may have contributed to antecedent myocardial hypertrophy and fibrosis that worsened perfusion, compromised compensatory functional mechanisms, and/or predisposed to arrhythmias in the post-MI period.

The current study, in combination with prior observational studies, provides strong support for well-designed clinical trials evaluating the benefit of aldosterone antagonists in preventing and/or slowing progression of seemingly separate cardiovascular disease processes. The current study supports a broad evaluation of aldosterone antagonists for treatment of acute MI, including patients with preserved systolic dysfunction. Prior observations lend support for studies of aldosterone blockade for a treatment of other cardiovascular disease processes, such as prevention of hypertension, preservation of renal function in the setting of chronic kidney disease, better control of resistant hypertension, slowing development of diastolic dysfunction, and even reducing risk of developing the metabolic syndrome. Assuming such broad benefits of aldosterone blockade seems grandiose, but prior interventional studies with aldosterone antagonists have confirmed that underneath much of the smoke surrounding aldosterone, there is true fire.
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David A. Calhoun

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