A growing body of evidence has related the existence of an excess of aldosterone and the development and progression of cardiovascular (CV) and renal disease. The list of processes where the mineralocorticoid is involved in an independent manner includes arterial hypertension, congestive heart failure, chronic kidney disease, coronary artery disease, and stroke.1

The association with aldosterone is particularly strong for arterial hypertension. The initial description by Conn2 of primary aldosteronism proved the existence of a direct relationship between elevated levels of aldosterone and the development of hypertension. Such an association was initially considered a rare cause of secondary hypertension, with a prevalence <1%. However, recent data indicate the possible existence of an unrecognized epidemic of primary aldosteronism. In fact, a prospective study by Rossi et al3 investigated a group of 1125 patients and, through a carefully performed protocol, concluded that 11.2% presented with a primary hyperaldosteronism. Primary aldosteronism implies excessive organ damage to the heart, vessels, and kidney, which facilitates a higher frequency of CV events,4 and if its real prevalence is higher than reported previously, its contribution to the final consequences of CV and renal disease in the hypertensive population could be very relevant.

The contribution of aldosterone to the development of arterial hypertension in the general population has been shown recently by the Framingham Offspring Study in which serum plasma aldosterone levels in normotensive subjects predicted subsequent increases in blood pressure and in the development of incident hypertension.5 A role of aldosterone in arterial hypertension is also suggested by the broad antihypertensive efficacy of mineralocorticoid receptor antagonists in treating unselected hypertensive patients, including those with resistant hypertension.6 The positive response of blood pressure to both eplerenone and spironolactone suggests the existence of a causative role of aldosterone in the development and maintenance of arterial hypertension. Similarly, a causative role of aldosterone in albuminuria and left ventricular hypertrophy, 2 common complications of arterial hypertension, can be derived from the regression of albuminuria and left ventricular hypertrophy in response to mineralocorticoid receptor blockers.7,8 The regression attained with the mineralocorticoid receptor blocker in both forms of target organ damage was similar to those obtained with suppression of the renin-angiotensin system and increased considerably with the combination of the 2 forms of therapy.

In the present issue of Hypertension, Pitt et al9 describe that, in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, use of eplerenone within 3 to 14 days of an acute myocardial infarction complicated by left ventricular systolic dysfunction and symptomatic heart failure was associated with significant reductions in the coprimary end points of all-cause mortality and CV hospitalization or CV mortality in patients with a history of hypertension. Patients without such a history did not exhibit significant reductions in these end points, although hospitalization for heart failure was significantly reduced in those patients receiving eplerenone. Interestingly, the authors discounted better blood pressure control as an explanation of the good results of the mineralocorticoid receptor blocker in the group of hypertensive patients. The authors concluded that postmyocardial infarction patients with left ventricular systolic dysfunction and heart failure should be risk stratified based on their previous history of hypertension. They recommend that those with a positive history of hypertension should be treated early with eplerenone to prevent death. In those patients without this antecedent, eplerenone should be started, to prevent later development of heart failure requiring hospitalizations, before hospital discharge.

Although the data of any posthoc analysis must be considered with caution, those in this article generate an interesting hypothesis that expands the relation between aldosterone and blood pressure and the potential need for a wider use of mineralocorticoid receptor blockers in arterial hypertension. It is well known that elevated blood pressure contributes importantly to the development of CV disease, including myocardial infarction. This risk is particularly elevated in patients with primary aldosteronism, but other forms of arterial hypertension can be initiated and maintained with the combination of the 2 forms of therapy.
stages of CV disease. The mechanisms by which aldosterone may worsen CV complications take place preferentially in the presence of a high salt intake and mainly consist of perivascular inflammation and fibrosis and myocardial hypertrophy and fibrosis. The existence of a cross-talk between aldosterone and angiotensin II has been described: aldosterone increases tissue angiotensin-converting enzyme and upregulates angiotensin receptors, suggesting the potential for a vicious circle in which angiotensin II potentiates aldosterone secretion, which, in turn, leads to an increase in angiotensin II generation and, therefore, to an additional increase in aldosterone. As can be seen in the Figure, the combination of new or existing therapies simultaneously blocking the effects of aldosterone and angiotensin II is needed.

As a conclusion of these considerations, ongoing and new trials evaluating the capacity of aldosterone antagonists in combination with angiotensin II blockade in preventing or retarding the progression of CV and renal disease are needed.

Disclosures
L.M.R. has served as advisor and speaker for Pfizer.

References
Aldosterone, Hypertension, and Cardiovascular Disease: An Endless Story

Luís M. Ruilope

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