EDITORIAL COMMENT

Should We Consider Aldosterone as the Primary Screening Target for Preventing Cardiovascular Events?

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There has been a growing literature on the genomic and non-genomic effects of aldosterone contributing to hypertension and cardiovascular diseases during the past decades (1). However, it was not until the recent publication of the Randomized Aldactone Evaluation Study (RALES) (2) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (3) that interest grew in the pharmacologic blockade of aldosterone receptors for cardiovascular protection. In animal studies, excessive aldosterone has been associated with collagen deposition, myocardial fibrosis, and myocardial remodeling (4). Blocking the synthesis or function of aldosterone also has been demonstrated to improve diastolic dysfunction in hypertensive patients with diastolic heart failure (5) and improve endothelial function in patients with asymptomatic left ventricular dysfunction or mild heart failure (6). Theoretically, aldosterone receptor antagonists are likely to be beneficial across a broad spectrum of cardiovascular diseases. However, to date, the use of spironolactone has been mostly restricted to patients with advanced heart failure (New York Heart Association functional class III or IV as in the RALES trial), severe ascites, or hyperaldosteronism in the absence of renal insufficiency. The EPHESUS study added patients with heart failure due to recent myocardial infarction to the mix, using the more selective aldosterone receptor blocker, eplerenone (3).

The case-control matching strategy is easily understood, and the authors have carefully matched known confounders that may influence the comparison. However, this matching strategy requires early decisions about which variables are confounders and which are predictors. There are risks of overmatching (i.e., matching on factors that are not necessarily confounders) as well as undermatching (i.e., unable to match confounding factors that are unknown or not documented, such as genetic predispositions and environmental factors). Furthermore, if the matching variable (such as single-time blood pressure measurement) is not fixed but could be modified by the predictor of interest (in this case, aldosterone), then the predictor itself could become a potential confounder and the interpretation may become difficult. Because serum aldosterone levels in the physiologic range can influence blood pressure when the levels are in the highest quartile (11), it is conceivable that serum aldosterone might act as a confounder. In addition, because only the prevalences of past cardiovascular events were compared between the groups, a causal relationship between excessive aldosterone and incident cardiovascular events could not be established. Despite all the caveats, the report by Milliez et al. (9) is provocative, and these results point to potential benefits of aggressive screening for and prevention of hyperaldosteronism in patients at risk of developing cardiovascular diseases.

How should we proceed? The findings of Milliez et al. (9) may not necessarily be novel, but if confirmed, might lead to a more widespread use of spironolactone or eplerenone for patients with hypertension—a concept that has continued to evolve (12) and can be extrapolated from the benefits of prescribing angiotensin-converting enzyme inhibitors for at-risk patients (13,14). The logical next step is to conduct a “proof-of-concept” mortality trial using aldosterone receptor antagonists as add-on therapy for primary prevention in patients with hyperaldosteronism. However, from the RALES and EPHESUS trials, it is clear that the potential benefits of aldosterone receptor blockade have to be balanced against the costs and the potential risks associated with the use of aldosterone-blocking drugs, particularly in elderly patients who are prone to hyperkalemia and renal insufficiency beyond the clinical trial setting (15). Furthermore, the impact of aldosterone receptor antagonists used in from a hypertension clinic, the authors found significantly more strokes, non-fatal myocardial infarction, and atrial fibrillation in hypertensive patients with primary hyperaldosteronism (whether it was due to aldosterone-producing adenoma or bilateral adrenal hyperplasia) than in a group of hypertensive patients without hyperaldosteronism who were matched for age, gender, and blood pressure. These findings add to the growing literature that excessive aldosteronism (detected in as many as 10% of patients with “essential hypertension” by careful hormonal evaluation) (10) may contribute to cardiovascular morbidity independent of elevated blood pressures.

The association between excessive aldosterone and cardiovascular morbidity in patients with hypertension was described many years ago (7). The careful screening of aldosterone-renin ratios has led to a 10-fold increase in the detection rate of primary aldosteronism (8). The report of Milliez et al. (9) in this issue of the Journal re-examines this relationship in the contemporary era. Using a matched case-control strategy in a relatively large patient population

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*Editorials published in the Journal of American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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the setting of widespread use of angiotensin-converting enzyme inhibitors or angiotensin receptor-blocking drugs remains to be carefully evaluated. Perhaps the larger question would be thus: is there ever going to be a change in the paradigm for cardiovascular prevention, whereby targeted routine screening (as in this case, careful identification of patients with hyperaldosteronism) allows tailoring of therapy? Here lies the greatest challenge of our time—we will inevitably need a concerted effort to develop innovative ways beyond polypharmacy and randomized controlled trials to translate clinical evidence into effective medical practices.

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