Aldosterone is the major mineralocorticoid in the human body and is produced in the zona glomerulosa of the cortex in the adrenal glands, and its secretion is stimulated by angiotensin II, adrenocorticotropic hormone, catecholamines, and local potassium levels. Its levels in plasma are elevated 4-fold in heart failure (HF). Through a variety of mechanisms, aldosterone is believed to play a role in the pathogenesis and progression of left ventricular dysfunction. The mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have consistently demonstrated a 20% reduction in mortality and 21% reduction in sudden death, which has been counterbalanced by a 6% to 12% risk of hyperkalemia (potassium >6.0 mEq/L) depending on the baseline estimated glomerular filtration rate.

In this issue of Circulation: Heart Failure, O’Meara and colleagues report on a retrospective analysis from the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial that tested rate versus rhythm control in patients with both atrial fibrillation and HF. In a carefully performed statistical model, the use of MRAs had a relative risk of 1.97 for death, P=0.001, which appeared to be independent from the atrial fibrillation strategy used, renal function, and the propensity to use MRAs in subjects in the trial. How do these results compare with prior HF trials? The Randomized Aldactone Evaluation Study (RALES) trial and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial did not report atrial fibrillation as a baseline characteristic; however, the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) trial reported in 30% with baseline atrial fibrillation that there was no interaction with MRAs. One possibility in AF-CHF trial is that the attempted propensity adjustment for the use of MRAs failed to account for the severity of illness in those who received those agents. Indeed, subjects who received MRAs had lower ejection fractions (P<0.0001), worse New York Heart Association functional classification (P<0.0001), lower estimated glomerular filtration rate (P<0.0124), greater use of diuretics and digoxin (P<0.0001), lower blood pressures (P<0.0001), and most importantly, a substantially higher rate of HF hospitalization in the preceding months before entering the trial (P<0.0001). The authors state that the results with and without propensity adjustments were similar, so those without adjustment are reported. This suggests that for some reason, an attempt to model physician selection for MRAs for an individual patient may have failed, and thus, MRA use in this data set is simply a proxy for more ill patients with higher overall mortality rates.

The results from this analysis, however, should be taken at face value with respect to the possibility that in HF patients with atrial fibrillation with high rates of antiarrhythmic drug use, MRA therapy was associated with 40% excess total and cardiovascular mortality, P=0.005, P=0.009, and a doubling of arrhythmic deaths, P≈0.001, with no effect on nonarrhythmic deaths or progression of HF. In the case of AF-CHF, the best suggestion is to have more detailed review of what happened in these arrhythmic deaths with respect to potassium and drug interactions, use of defibrillators, and changes in renal function. In the 183 who had follow-up data, the potassium level did not seem related to total or cardiovascular mortality, worsening HF, or arrhythmic deaths. The use of cardioselective defibrillators was 77% at baseline, with no information on the subsequent implantation during the course of the trial. Perhaps, a case-by-case review of particularly the arrhythmic deaths would give clues on the events that occurred and whether any circumstances could be attributed to the use of MRAs.

In summary, we simply do not have enough information to implicate MRAs in the risks of adverse outcomes in patients with both atrial fibrillation and HF. It is clear from the baseline data that more ill patients with higher expected event rates received MRAs. Future studies should carefully evaluate the dynamic changes in potassium, renal function, and the use of both drugs and procedures to manage atrial fibrillation and HF to gain a better understanding of the risks and benefits of MRAs in this HF subset.

Disclosures
None.

References


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