EDITORIALS

Aldosterone Antagonists — Last Man Standing?

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The transformation of cardiac care over the past half century has been breathtaking to witness. In large part, this transformation is due to the advent of new drugs and devices, improved health care systems, and behavioral modifications such as smoking cessation. Four cardiac medicines developed before 1960 that survived the turn of the millennium are aspirin, digoxin, warfarin, and spironolactone. New competitors threaten the continued longevity of aspirin, the survival of digoxin depends on evidence of its ability to improve exercise tolerance and quality of life in patients with heart failure, and new pretenders for warfarin are here. Remarkably, after over 50 years, the aldosterone antagonism achieved by spironolactone (and more recently eplerenone) has earned an enduring role in the treatment of heart failure.[1]

When spironolactone was developed, it was a minor player complementing more powerful diuretics in achieving volume homeostasis. Our understanding of heart failure was then predominantly focused on hemodynamic perturbations. As long ago as 1960, the drug was found to protect rats against myocardial necrosis,[2] yet this observation languished for decades. Subsequently, two parallel tracks of knowledge emerged, which are germane to a resurgence of interest in antagonizing aldosterone. The first track involves the complex adaptations affecting the failing and remodeled heart. Cardiac enlargement and increased sphericity are often accompanied by scarring and fibrosis. Neurohormonal activation and altered vascular compliance of coronary and peripheral blood vessels compound this unfavorable milieu.[3] The second track concerns the pleiotropic effects of aldosterone antagonists. These include conservation of potassium and magnesium, the depletion of which potentiates ventricular arrhythmias and sudden death; inhibition of fibroblast proliferation and perivascular fibrosis, which are promoted by chronic hyperaldosteronism; and reversal of unfavorable coronary and renal vascular remodeling, which is modulated by endothelial-cell and baroreceptor dysfunction.[3]

These physiological observations now appear to have important clinical consequences. In the Randomized Aldactone Evaluation Study (RALES), Pitt and colleagues[4] demonstrated that spironolactone therapy could significantly reduce rates of death and hospital readmission for worsening heart failure among patients with functional class III or IV heart failure. Four years after this seminal study, the same investigators conducted the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[5] which showed that eplerenone, a selective aldosterone-receptor blocker, reduced morbidity and mortality among patients recovering from acute myocardial infarction with complicating left ventricular dysfunction. As a result of these convincing findings, aldosterone-receptor blockade has become part of recommended therapy in such patients.[6]

In this issue of the *Journal*, Zannad and colleagues[7] complete an aldosterone-trial trilogy with their report on the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF; ClinicalTrials.gov number, NCT00232180), which shows that eplerenone reduces the rate of death from cardiovascular causes or hospitalization for heart failure by approximately 37%, as compared with placebo, in patients with functional class II heart failure. Although this effect seems surprisingly large for a trial of mildly symptomatic patients, careful review of the baseline characteristics is instructive.

The majority of the study patients were heart disease veterans: one half had previously been hospitalized for heart failure and had a history of myocardial infarction; hypertension, atrial fibrillation, and diabetes were also common. The mean ejection fraction of 26% (nearly identical to that in the more severely symptomatic patients in RALES) is a cogent reminder of the discordance between functional class and left ventricular function. An additional feature marking the EMPHASIS-HF patients as high risk is that approximately one quarter had left bundle-branch block, and the overall mean QRS duration was 122 msec (with one quarter having a QRS duration >130 msec). Although the concomitant use of beta-blockers and angiotensin-converting–enzyme inhibitors was common, the infrequent use of implantable defibrillators or cardiac resynchronization therapy raises the question of whether eplerenone would have fared as impressively had a larger proportion of the study population received implantable electrical devices, in alignment with current guidelines.[6] This points to the need for further investigation, given that even the trial participants receiving active therapy had a 1-year mortality rate of approximately 5.0%.

The effect on death from cardiovascular causes or hospitalization for heart failure translates into an impressively low number needed to treat: 19 patients. The number needed to treat to prevent one death is 51 patients, positioning this therapy in the front rank of therapeutic choices. The survival curves invite speculation about whether the effect of eplerenone on volume homeostasis came into play early, thereby affecting hospitalization for heart failure sooner, whereas structural changes such as favorable cardiac remodeling might have accounted for the more delayed reduction in mortality.

The EMPHASIS-HF investigators have added real value to the management of heart failure. Since spironolactone is available for pennies a day, one might reasonably ask whether the greater cost of eplerenone is warranted or whether it is reasonable to simply assume that the current findings also apply to spironolactone and reserve the newer, more expensive therapy for those few patients in whom the side effects of spironolactone are disabling. I believe this would be a reasonable tactic. It is now time to overcome undertreatment by ensuring that this form of therapy is incorporated into all heart-failure regimens.[8] It is incumbent on the prescriber to perform appropriate monitoring of renal and electrolyte status, which can enhance the safety of such treatment.[9]

As one reflects on the EMPHASIS-HF results, the question arises: Do they open doors for investigating aldosterone antagonism in other cardiovascular diseases? The answer is, most emphatically, yes. In fact, studies of this therapy in patients with diastolic dysfunction and acute myocardial infarction are ongoing, and the results are eagerly awaited. A preventive approach in patients at high cardiovascular risk might even be on the horizon.[10] Of the quartet of therapies that have served us well over the past half century, aldosterone antagonism seems most likely to be the last man standing.

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