Consensus

Update on Aldosterone Antagonists Use in Heart Failure With Reduced Left Ventricular Ejection Fraction Heart Failure Society of America Guidelines Committee

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ABSTRACT

Aldosterone antagonists (or mineralocorticoid receptor antagonists [MRAs]) are guideline-recommended therapy for patients with moderate to severe heart failure (HF) symptoms and reduced left ventricular ejection fraction (LVEF), and in postmyocardial infarction patients with HF. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial evaluated the MRA eplerenone in patients with mild HF symptoms. Eplerenone reduced the risk of the primary endpoint of cardiovascular death or HF hospitalization (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54−0.74, $P < .001$) and all-cause mortality (adjusted HR 0.76, 95% CI 0.62−0.93, $P < .008$) after a median of 21 months. Based on EMPHASIS-HF, an MRA is recommended for patients with New York Heart Association (NYHA) Class II−IV symptoms and reduced LVEF (<35%) on standard therapy (Strength of Evidence A). Patients with NYHA Class II symptoms should have another high-risk feature to be consistent with the EMPHASIS-HF population (age >55 years, QRS duration >130 msec [if LVEF between 31% and 35%], HF hospitalization within 6 months or elevated B-type natriuretic peptide level). Renal function and serum potassium should be closely monitored. Dose selection should consider renal function, baseline potassium, and concomitant drug interactions. The efficacy of eplerenone in patients with mild HF symptoms translates into a unique opportunity to reduce morbidity and mortality earlier in the course of the disease. (*J Cardiac Fail 2012;18:265−281*)

Key Words: Aldosterone antagonists, eplerenone, heart failure, spironolactone.

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Manuscript received February 12, 2012; revised manuscript accepted February 15, 2012.

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This article was reviewed and approved by the HFSA Executive Council on February 20, 2012. The HFSA Executive Council members are listed in the Acknowledgment.

See page 278 for disclosure information.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2012.02.005

Aldosterone receptor antagonists, also referred to as mineralocorticoid receptor antagonists (MRA), are currently guideline-recommended evidence-based therapy for select patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF).[1] The contribution of aldosterone to the development and progression of HF is well-established (Table 1).[2–6] Further, large randomized, controlled clinical trials of aldosterone receptor antagonists showed that spironolactone improved survival in patients with severe HF with depressed EF,[7] and eplerenone reduced morbidity and mortality in postmyocardial infarction (MI) patients with HF and LV dysfunction.[8] The Heart Failure Society of America (HFSA) and other national and international guidelines therefore recommend the use of aldosterone receptor antagonists in HF patients similar to the populations studied in the Randomized Aldactone Evaluation study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trials (Table 2).[1,7–10] These trials excluded patients with mild HF symptoms, rendering a knowledge gap regarding the efficacy and safety of aldosterone receptor antagonists in this specific population.

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial was designed to address this knowledge gap.[11] The data generated from this study necessitates a reexamination of the current guideline recommendations. The purpose of this article is to evaluate the existing and new evidence for aldosterone antagonism in patients across the spectrum of HF, and to provide suggestions for how clinicians may incorporate this evidence into their clinical practice. This document is not a formal guideline update, but rather a document to communicate latest results, cumulative evidence, highlight persistent knowledge gaps, and provide care recommendations related to aldosterone antagonism in HF in accordance with emerging evidence.

Table 1. Pleiotropic Effects of Aldosterone in Heart Failure*

Heart
• Myocyte hypertrophy
• Interstitial fibrosis
• Coronary atherosclerosis
• Decreased natriuretic peptide synthesis
• Reduced norepinephrine uptake
Kidney
• Sodium and water retention
• Potassium and magnesium wasting
• Glomerulosclerosis
• Tubulointerstitial fibrosis
• Podocyte apoptosis and proteinuria
Vasculature
• Endothelial cell hypertrophy
• Vascular smooth muscle cell hypertrophy
• Atherosclerosis
• Reduced nitric oxide bioavailability
• Vasomotor dysfunction
• Platelet aggregation

*Oxidative stress and inflammation have been shown to play a pathophysiologic role in all systems.[20]

Pathophysiology of Aldosterone in HF

More than 50 years ago, Luetscher and Johnson[12] first observed that adults and children with HF secrete a steroid hormone in the urine with sodium-retaining properties. Using selective venous sampling and liquid chromatography, Davis et al[13] then identified this hormone as aldosterone and found that it was produced in excess in the adrenal gland in edematous states. Subsequent studies have shown that plasma aldosterone levels are elevated in patients with HF despite maximal renin-angiotensin system blockade (so-called aldosterone escape),[14] correlate with disease severity,[15] and predict mortality.[16] These data suggested that aldosterone is not simply a biomarker of disease activity, but a potent mediator of ventricular and vascular remodeling and disease progression.

Elevated plasma concentrations of aldosterone are due to both increased adrenal production and decreased hepatic clearance.[17] In patients with HF, major triggers of aldosterone release include angiotensin II (especially when intravascular volume is reduced with diuretic therapy), serum potassium concentration, and corticotropin.[18] Additional stimuli that play a minor role in normal adults but are upregulated in HF include circulating arginine vasopressin, catecholamines, and endothelin. Aldosterone has pleiotropic effects on the heart, kidney and the vasculature (Table 1). In the myocardium, aldosterone exerts growth-promoting and pro-fibrotic effects on myocytes and the interstitium, respectively. Transgenic mouse models demonstrate that cardiac-specific overexpression of 11β-hydroxysteroid dehydrogenase type 2 with activation of mineralocorticoid receptors leads to concentric ventricular remodeling, myocardial fibrosis and premature death.[19] This phenotype can be attenuated and survival enhanced with aldosterone receptor blockade. Reduction in dietary salt intake may also play a key role in limiting aldosterone-mediated cardiovascular damage.[20]

Beyond the adrenal cortex, aldosterone is produced by vascular endothelial cells where it promotes inflammation and fibrosis leading to endothelial dysfunction. Relevant to patients with ischemic HF, stimulation of mineralocorticoid receptors in the coronary and peripheral arteries also exerts proatherogenic effects, which are accelerated by downregulation of the inhibitory enzyme 11β-hydroxysteroid dehydrogenase type 2.[21] Numerous studies in animals and humans have demonstrated salutary effects of aldosterone receptor blockade on vasomotor reactivity,[22] baroreceptor responsiveness,[23] and norepinephrine uptake. Myocardial injury can be attenuated by inhibiting the development of coronary inflammatory lesions.[24] These experimental data provide an explanation for reduction in both HF and sudden death mortality demonstrated in RALES, EPHESUS, and EMPHASIS-HF.[7,8,11]

In the kidney, aldosterone has long been understood to promote reabsorption of sodium and water from tubular fluid, an effect that is regulated by the α-subunit of the