Roles of Aldosterone Receptor Antagonists in Heart Failure, Hypertension, and Chronic Kidney Disease

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ABSTRACT

Aldosterone receptor antagonists (AAs) antagonize the aldosterone hormone and prevent sympathetic activation, parasympathetic inhibition, and myocardial remodeling. In heart failure with reduced ejection fraction, AAs may be considered in patients who are symptomatic despite optimal doses of angiotensin-converting enzyme inhibitors and beta blockers, but it should not be used in the management of patients with preserved ejection fraction without other cormorbidities. AAs may be considered as an add-on in patients with inadequate control of blood pressure or in patients with primary hyperaldosteronism. Insufficient evidence is available for using AAs in chronic kidney disease patients.

Keywords: chronic kidney disease, eplerenone, heart failure, hypertension, spironolactone

Medications that antagonize the aldosterone hormone are useful for specific patient populations. Aldosterone stimulates sodium retention, magnesium, and potassium loss. Additionally, excess aldosterone has been associated with impaired insulin sensitivity and impaired glucose tolerance and can further elevate patients' risks of metabolic syndrome and cardiovascular (CV) disease.[1,2] Aldosterone receptor antagonists, also known as mineralocorticoid receptor antagonists, block the mineralocorticoid receptor, which is the target site for aldosterone. Examples of aldosterone receptor antagonists include spironolactone and eplerenone.[3] In the kidney, aldosterone receptor antagonists inhibit sodium reabsorption and potassium excretion. Low doses of aldosterone receptor antagonists have minimal diuretic effects, but the potassium-sparing effects can be significant, resulting in hyperkalemia. Spironolactone is a nonselective aldosterone receptor antagonist that also interacts with androgen and progesterone receptors; this may lead to gynecomastia (2.5%–10% for spironolactone and < 1% for eplerenone) and impotence (< 1% for both) in some patients.[4–6] These side effects are less common with eplerenone because it is a selective aldosterone receptor antagonist with low affinity for the progesterone and androgen receptors.[7–9] Because aldosterone receptor antagonists have a variety of indications and can cause side effects, nurse practitioners (NPs) should be knowledgeable with this group of medications for daily practice. This article describes various roles of aldosterone receptor antagonists for the management of heart failure, hypertension, and kidney disease and helps guide NPs to use aldosterone receptor antagonists appropriately for patients.

DISCUSSION

Heart Failure

Heart failure (HF) occurs when the heart fails to pump and provide adequate perfusion to the peripheral organs. HF is commonly categorized as HF with reduced left ventricular ejection fraction

(HFrEF) or HF with preserved left ventricular ejection fraction (HFpEF). HFrEF occurs primarily because of diminished cardiac contractility, leading to decreased left ventricular ejection fraction (EF) (40% or less).[3,10] HFpEF occurs primarily because of diminished cardiac relaxation, leading to elevated left ventricular filling pressure and decreased end-diastolic volume. Definitions for HFpEF vary; it is generally defined as EF greater than 40%, 45%, 50%, or 55%.[10] In both cases, cardiac output declines, which reduces peripheral perfusion and oxygenation of organs.[3]

Because of inadequate perfusion and oxygenation of the organs, the kidneys activate the renin-angiotensin-aldosterone system to reabsorb sodium and water, increase plasma volume, and increase cardiac output. Increased aldosterone levels induce myocardial remodeling, thereby increasing rigidity of the myocardium and further impairing the heart's ability to contract and relax adequately. As a result, activation of the renin-angiotensin-aldosterone system further worsens HF symptoms, such as peripheral edema and pulmonary congestion, as well as accelerates HF progression.[3] Aldosterone receptor antagonists antagonize the effects of aldosterone at aldosterone receptors in the collecting tubules of the kidney and at various other target tissues. This results in increased salt and water excretion, which reduces plasma volume, and in the prevention of cardiac remodeling.[11] Several trials have proven that aldosterone receptor antagonists reduce risks of mortality in HFrEF patients.[4,5,12] Evidence on the efficacy of aldosterone receptor antagonists in HFpEF is scarce.[6,13]

HFrEF. According to the 2013 American College of Cardiology Foundation/American Heart Association guideline, aldosterone receptor antagonists can be added to angiotensin-converting enzyme inhibitors (ACEis) and beta blockers in patients with HFrEF and New York Heart Association (NYHA) functional classes II through IV symptoms. Patients can only be initiated on aldosterone receptor antagonists if the estimated creatinine clearance is above 30 mL/min and the serum potassium concentration is below 5 mEq/dL.[10]

The efficacy of aldosterone receptor antagonists in HFrEF was investigated in the Randomized Aldactone Evaluation Study (RALES), the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS) trials.[4,5,12] RALES studied the efficacy of spironolactone, whereas EPHESUS and EMPHASIS focused on eplerenone. RALES enrolled patients with an EF of 35% or less and NYHA classes III or IV symptoms. Patients who took spironolactone experienced significantly lower rates of death from any cause, death from cardiac cause, and hospitalization for cardiac causes. Incidences of gynecomastia or breast pain were significantly higher with spironolactone use (spironolactone 10% vs placebo 1%, $P < .001$).[4] EPHESUS focused on patients with a recent history of acute myocardial infarction and left ventricular dysfunction. EMPHASIS focused on patients with reduced EF (< 30%) and mild HF symptoms (NYHA functional class II). For both trials, eplerenone significantly decreased the risks of mortality and hospitalization. However, eplerenone increased the risks of hyperkalemia. Incidences of gynecomastia and impotence were similar between eplerenone and placebo.[5,12]

Spironolactone was shown to decrease mortality and hospitalization in the RALES study. The EPHESUS and EMPHASIS trials have shown that eplerenone is effective for reducing the risks of mortality and morbidity. Both eplerenone and spironolactone may increase serum potassium concentration. Because most HF patients take ACEis and/or angiotensin receptor blockers (ARBs), giving aldosterone receptor antagonists to HF patients further exacerbates the risks of hyperkalemia. Spironolactone may significantly increase the risks of gynecomastia. When managing HF patients, cardiologists should be initially consulted to ensure appropriate management. NPs need to have a thorough understanding of aldosterone receptor antagonists and the roles of aldosterone receptor antagonists in the management of HFrEF to ensure optimal outcomes. While on aldosterone receptor antagonists, NPs must monitor patients closely for electrolyte changes and signs of breast pain.