What Evidence is Available on Aldosterone Antagonists for Use in Heart Failure with Preserved Ejection Fraction?

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**Question:** What evidence is available on aldosterone antagonists for use in heart failure with preserved ejection fraction?

**Answer:**

**Introduction**

Heart failure (HF) is primarily caused by abnormalities in cardiac systolic or diastolic function, which dictate the prevalence, prognosis, and pharmacotherapy used to treat the patient. Diastolic heart failure can be referred to using several interchangeable terms such as HF with normal ejection fraction, diastolic dysfunction, or the newest terminology being HF with preserved ejection fraction (HFpEF). HFpEF is accountable for over half of HF patients and its prevalence depends on various factors, with age being the most important determinant. Several large, randomized, multi-center, double-blinded trials have been conducted to create guidelines for systolic HF treatment, which is also known as HF with reduced ejection fraction (HFrEF). In contrast, few trials have been published on the treatment of HFpEF. Currently, the Heart Failure Society of America (HFSA) 2010 guidelines recommend the use of diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers as possible treatments for HFpEF.

While there are options for the treatment of HFpEF, most of the currently suggested medications for treatment have grade C recommendations, which are based on “expert opinion, epidemiologic findings from observational studies, and safety findings from large-scale use” unless specifically indicated for a compelling indication. The lack of concrete evidence and treatment recommendations for HFpEF signals a further need for other therapy options, leading to the investigation of aldosterone antagonists as a potential treatment option.

Studies have demonstrated that the mineralocorticoid aldosterone is stimulated by angiotensin II and activates mineralocorticoid receptors to cause sodium retention, potassium excretion, endothelial dysfunction, vascular inflammation, hypertrophy, and fibrosis—all mechanisms that contribute to the pathophysiology of HF. Despite the use of ACEIs in HF treatment, aldosterone levels may still potentially increase, indicating that ACEIs may not fully suppress angiotensin formation. Increased levels of aldosterone have been associated with impaired functional capacity, decreased ventilator response during exercise, and an increase in cardiovascular mortality, making aldosterone a potential target for HF treatment. The 2 most commonly used aldosterone antagonists are spironolactone and eplerenone. Spironolactone (Aldactone®) is generically available and is a nonselective aldosterone receptor antagonist. Its nonselectivity is associated with the adverse effect of gynecomastia. Eplerenone (Inspra®) is a spironolactone derivative, is not yet available as a generic, and has higher selectivity for the mineralocorticoid receptor with less binding to androgen and progesterone receptors compared to spironolactone.

Aldosterone antagonists have been proven to be effective in the treatment of HFrEF in the Randomized Aldactone Evaluation Study (RALES) trial, demonstrating a 31% decrease in cardiovascular mortality and a 30% risk reduction in all-cause mortality in the spironolactone treatment group compared to placebo. Similarly, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial evaluated death from cardiovascular causes and hospitalization for HF as the primary outcome in which the eplerenone treatment group experienced a significantly decreased incidence (18.3% eplerenone group vs. 25.9% control group). The treatment group also had a statistically significant 38% reduction in hospitalizations for HF and demonstrated a decrease in all-cause mortality in comparison to the control group. The HFSA 2010 guidelines strongly recommend (grade A) the use of an aldosterone antagonist for New York Heart Association (NYHA) class IV HF with left ventricular ejection fraction (LVEF) < 35% in addition to standard therapy classified as ACEI/ARB and beta-blocker therapy. While the RALES and EMPHASIS-HF trials have demonstrated a place for aldosterone antagonists in HFrEF treatment, aldosterone antagonists have not been included in HFpEF treatment guidelines yet. Spironolactone and eplerenone have been further investigated as options for HFpEF treatment in 3 clinical trials over the past 2 years.

**Clinical Trials**

The RAAM-PEF (Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction) trial was a randomized, double-blinded, placebo-controlled, single-center study conducted by Deswal et al. comparing eplerenone 25-50 mg to placebo over 24 weeks in 44 patients. Investigators determined that a sample size of 21 patients in each group was necessary to provide 85% power with a 2-tailed α level of 0.05 in order to detect differences in endpoints. The primary endpoint was defined as a change in 6-minute walk distance (6MWD) from baseline after the 24 weeks of randomization and treatment. The 6MWD measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes to determine functional capacity and is predictive of hospitalization rates and mortality in HF patients. Secondary endpoints included echocardiographic measurements of diastolic dysfunction, biomarkers such as collagen turnover and B-type natriuretic peptide, HF-related quality of life using the Kansas City Cardiomyopathy Questionnaire, and NYHA class.
The results of this study showed an improvement in the primary endpoint of 6MWD in both placebo and treatment groups, although the difference was not significant (p = 0.91). Similarly, all secondary endpoints were not found to be statistically significant with the exception of the E/E’ ratio and amino-terminal peptide of procollagen type I (PINP) and carboxyl-terminal telopeptide of collagen type I (CITP) biomarkers. The E/E’ ratio, which measures left ventricular filling pressure and is regarded as the best index for detecting diastolic dysfunction in HFpEF, was significantly decreased in the eplerenone group (p = 0.01) compared to the placebo group, which demonstrated an increase in the E/E’ ratio. The PINP and CITP biomarkers evaluate collagen turnover and are used as noninvasive markers to monitor the regression of myocardial fibrosis. At baseline versus 24 weeks in the eplerenone group, both PINP and CITP levels were significantly decreased (p = 0.009 and p = 0.026, respectively). The trial concluded that although eplerenone treatment in patients with HFpEF did not improve exercise capacity as measured through the 6MWD test, it did result in beneficial changes to collagen turnover and diastolic function.

The Aldo-DHF (The Aldosterone Receptor Blockade in Diastolic Heart Failure) trial was a randomized, double-blinded, placebo-controlled, prospective, multi-center trial conducted by Edelmann et al. comparing spironolactone to placebo. Four hundred thirty-three patients were randomized to receive spironolactone 25 mg or placebo and were followed for approximately 12 months. Type I and II error rates were set at 0.05 (α) and 0.1 (β), respectively, with a power of 90% and an estimated sample size of 420 patients. The co-primary endpoints compared spironolactone therapy to placebo on diastolic function (E/E’ ratio) and maximal exercise capacity (peak VO2) during cardiopulmonary exercise testing in patients with HFpEF. Peak VO2 was defined by the study as the maximum value of the last three 10-second averages during exercise. Secondary endpoints included echocardiographic measures of cardiac function and remodeling, submaximal and maximal exercise capacity, serum biomarkers, quality of life, morbidity, and mortality.

The results of the Aldo-DHF trial showed an improvement in the primary endpoint of diastolic dysfunction as measured by the E/E’ ratio. Echocardiographic results of the treatment group showed a decrease in the E/E’ ratio after 12 months compared to placebo (95% CI, -2.0 to -0.9, p < 0.001). The primary endpoint of maximal exercise capacity did not differ significantly between the treatment and placebo group after 12 months (p = 0.81). Other secondary endpoints of note in the spironolactone group versus placebo group included an increase in LVEF (95% CI, 0.1 to 3.1, p = 0.04), increase in 6MWD (95% CI, -27 to -2, p = 0.02), decrease in left ventricular mass index (95% CI, -10 to -1, p = 0.009), and decrease in left ventricular end diastolic diameter (95% CI, -2.5 to -0.3, p = 0.01). The study also acknowledged that it was not adequately powered to assess the secondary endpoints of morbidity and mortality. The trial concluded that spironolactone treatment in HFpEF patients improved diastolic function and left ventricular function but had no effect on maximal exercise capacity.

The clinical study TOPCAT (Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) is a multi-center, international, randomized, double-blinded, placebo-controlled trial using 15-45 mg of spironolactone. The study was conducted with 3,445 subjects aged 50 years or older, recruited from over 200 clinical centers, with HF and LVEF ≥ 45%, HFpEF, controlled systolic blood pressure, and a serum potassium < 5.0 mEq/L. The primary endpoint was a composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF. Secondary endpoints included all-cause mortality, new onset of diabetes mellitus or atrial fibrillation, and quality of life. The study ended in January of 2012 and the results are expected to be published in the near future.

Discussion

The RAAM-PEF and Aldo-DHF trials found that aldosterone antagonist use in patients with HFpEF improved diastolic dysfunction as measured by the E/E’ ratio. However, according to the Aldo-DHF trial, there is currently no accepted minimal clinically important difference in E/E’ that should be achieved to alter the prognosis of HFpEF. Both trials also studied exercise capacity as measured by the 6MWD. The RAAM-PEF trial, which evaluated patients after 6 months of therapy, did not find a statistically significant difference between the eplerenone and placebo group while the Aldo-DHF trial, which evaluated patients after 12 months, found a marked improvement in the spironolactone group. The difference in these results may be attributed to the length of the 2 trials in which the RAAM-PEF trial may not have had adequate time for eplerenone to exert a clinical effect on 6MWD. It is also important to note that the RALES and EMPHASIS-HF trials evaluated aldosterone antagonists in HFrEF patients through the primary outcomes of differences in morbidity and mortality. In contrast, the RAAM-PEF and Aldo-DHF trials were only able to evaluate surrogate markers of morbidity and mortality in HFpEF such as diastolic function and exercise capacity.

In addition, the populations in both trials consisted mainly of NYHA class II patients. Therefore, the results of these studies may not be generalizable to sicker populations in the NYHA class III and IV categories. Also, RAAM-PEF was studied at the Veterans Affairs Medical Center in Houston, Texas, and all but 3 patients were male, indicating that the results are most applicable to men.

There is also concern with the risk of hyperkalemia because a major adverse effect of aldosterone antagonists is an elevation in potassium levels. Most, if not all, HF patients’ medication lists include an ACEI/ARB to prevent cardiac remodeling. The combination of an ACEI/ARB with an aldosterone antagonist may potentially increase the risk of an elevated potassium level leading to hyperkalemia and subsequent arrhythmias. In both trials, a nonstatistically significant difference was found between groups in the development of hyperkalemia, defined as a serum potassium ≥ 5.5 mEq/L. Thus, it can be concluded that with appropriate
and routine laboratory monitoring of serum potassium levels, aldosterone antagonists can be safely used in HFpEF patients who are on concurrent ACEI/ARB therapy.

Based on the evidence provided by RAAM-PEF and AldoDHF, an aldosterone antagonist may be a potential additive therapy for HFpEF if the patient’s blood pressure and heart rate are controlled and serum potassium levels are carefully monitored. While these trials have shown improvement in diastolic function and potential increases in exercise capacity, the effects of aldosterone antagonists on the long-term morbidity and mortality of HFpEF patients still remains to be seen as investigated through the TOPCAT trial. The results of the TOPCAT trial will provide more evidence about aldosterone antagonist use in HFpEF due to its clinical endpoints.

References