

Special Edition
"Heart Failure"

Review

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Treatment of Heart Failure With Aldosterone Antagonist Therapy

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ABSTRACT

This article discusses the clinical trial data for the treatment of heart failure with a reduced left ventricular ejection fraction (HFrEF) with an aldosterone antagonist. The American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines recommend with a class I indication the addition of an aldosterone antagonist in selected patients with New York Heart Association (NYHA) class II to IV HFrEF who can be carefully monitored for preserved renal function and normal serum potassium concentration. Patients treated with an aldosterone antagonist should have a serum creatinine 2.5 mg/dL or lower in men and 2.0 mg/dL or lower in women, and the serum potassium should be less than 5.0 mEq/L. This article also discusses the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOP-CAT) trial which randomized 3,445 patients with symptomatic heart failure with preserved ejection fraction (HFpEF) to receive either spironolactone 15 mg to 45 mg daily or placebo. Of these patients, 51% were from the Americas, and 49% were from Russia and Georgia. In the Americas group, compared with placebo, spironolactone decreased the primary outcome 18%, decreased cardiovascular mortality 26%, decreased hospitalization for heart failure 18%, decreased recurrent heart failure 25%, insignificantly decreased all-cause mortality 17%, had a 60% increased incidence of doubling of serum creatinine, had a similar incidence of serum creatinine ≥ 3.0 mg/dL, increased hyperkalemia 3.46 times, and reduced hyokalemia 49%. In the Russia and Georgia group, all of these outcomes were similar for patients treated with spironolactone or placebo.

KEYWORDS: Heart failure with reduced ejection fraction; Heart failure with preserved ejection fraction; Aldosterone antagonist; Spironolactone; Eplerenone.

In patients who have congestive heart failure, activation of the renin-angiotensin-aldosterone system is maladaptive.¹ Aldosterone stimulates renal and extrarenal sodium and water retention and reduces potassium excretion. Aldosterone contributes to progression of heart failure by vascular remodeling of the heart and other organs. Aldosterone contributes to fibroblast growth and excess collagen, causing structural remodeling of the myocardium. Aldosterone-induced myocardial fibrosis can contribute to ventricular dysfunction. This article will discuss the use of aldosterone antagonists in the treatment of heart failure with reduced left ventricular ejection fraction (HFrEF) and in the treatment of heart failure with preserved left ventricular ejection fraction (HFpEF).

HEART FAILURE WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION

The Randomized Aldactone Evaluation Study (RALES) was a double-blind study which randomized 1,663 patients, mean age 65 years, with New York Heart Association (NYHA) class III or IV HFrEF and a left ventricular ejection fraction (LVEF) $\leq 35\%$ treated with an angiotensin-converting enzyme (ACE) inhibitor, a loop diuretic, 74% with digoxin, and 10% with beta blockers to 25 mg of spironolactone daily or to placebo.² The primary endpoint was all-cause mortality. At 2-year follow-up, spironolactone 25 mg daily reduced mortality by 30% from 46% to 35% and hospitalization for worsening HFrEF by 35%.² In addition, patients treated

with spironolactone had a significant improvement in symptoms assessed by NYHA functional class.² In the RALES trial, the number of patients who received beta blockers was only 10%, and 74% of patients were treated with digoxin. The use of digoxin probably did not affect the results. The low use of beta blockers may have influenced the results.

Data from the RALES trial showed that high baseline serum levels of markers of cardiac fibrosis synthesis were associated with an increased risk of death or heart failure hospitalization and decreased with spironolactone treatment.³ The benefit in clinical outcomes with use of spironolactone treatment was associated with higher levels of collagen synthesis markers.³ Data from the RALES trial also showed that spironolactone reduced circulating levels of natriuretic peptides.⁴

Spironolactone was shown to improve left ventricular volumes and function at 1 year follow-up in 104 patients with chronic HFrEF randomized to spironolactone or to a control group.⁵ Spironolactone also increased exercise tolerance in these patients who were treated with spironolactone 50 mg daily for 1 year.⁵

After publication of the RALES trial, the prescription rate for spironolactone in patients recently hospitalized for heart failure in patients aged 66 years and older in Ontario, Canada increased from 34 per 1,000 patients in 1994 to 149 per 1,000 patients by late 2001.⁶ The incidence of hospitalization for hyperkalemia increased from 2.4 per 1,000 patients in 1994 to 11.0 per 1,000 patients in 2001, and the associated mortality increased from 0.3 per 1,000 patients in 1994 to 2.0 per 1,000 patients in 2001.⁶ In another study of 104 patients with heart failure in which spironolactone was used inappropriately without consideration of NYHA class and LVEF and without optimal background therapy with ACE inhibitors and beta blockers, 25% of patients developed hyperkalemia, 12% developed a serum potassium level of ≥ 6.0 mEq/L, and 25% developed renal insufficiency.⁷

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS) was a double-blind study which randomized 6,632 patients, mean age 64 years, with acute myocardial infarction complicated by HFrEF to eplerenone 25 mg initially titrated to a maximum of 50 mg daily or to placebo.⁸ The mean left ventricular ejection fraction (LVEF) was 33% in both treatment groups. In this study, 87% of patients were treated with an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin receptor blocker, 75% with a beta blocker, and 61% with diuretics. At 16-month mean follow-up, eplerenone reduced mortality by 15% from 554 deaths on placebo to 478 deaths on eplerenone and death from cardiovascular causes or hospitalization for cardiovascular events by 17% from 483 on placebo and 407 on eplerenone.⁸ Eplerenone reduced sudden cardiac death by 21%. The incidence of serious hyperkalemia was 5.5% in patients treated with eplerenone *versus* 3.9% in patients treated with placebo. The incidence of

hypokalemia was 8.4% in patients treated with spironolactone *versus* 13.1% in patients treated with placebo.⁸

At 30 days after randomization in the EPHESUS trial, eplerenone 25 mg daily reduced all-cause mortality by 31% from 4.6% on placebo to 3.2% on eplerenone and insignificantly reduced cardiovascular death and cardiovascular hospitalization by 13% from 9.9% on placebo to 8.6% on eplerenone.⁹ Eplerenone also reduced cardiovascular death by 32% from 4.4% on placebo to 3.0% on eplerenone and sudden cardiac death by 37% from 1.4% on placebo to 0.9% on eplerenone.⁹ The survival effects from use of eplerenone were independent from its diuretic and potassium-sparing effects.¹⁰

In the EPHESUS trial, patients were excluded if the baseline serum potassium was greater than 5.0 mEq/L or if the serum creatinine was greater than 2.5 mg/dL.¹¹ In this study, treatment with eplerenone caused an absolute increase in the incidence of a serum potassium of greater than 5.5 mEq/L of 4.4% and an absolute increase in the incidence of a serum potassium of greater than 6.0 mEq/L of 1.6% and an absolute decrease in hypokalemia (serum potassium less than 3.5 mEq/L) of 4.7%.¹¹

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial was a double-blind trial which randomized 2737 patients, mean age 68.7 years, with NYHA class II HFrEF with a LVEF $\leq 35\%$ to eplerenone up to 50 mg daily or placebo.¹² At 21-month median follow-up, the primary endpoint of cardiovascular death or hospitalization for heart failure was reduced 37% by eplerenone from 25.9% on placebo to 18.3% on eplerenone.¹² All-cause mortality was reduced 24% by eplerenone from 15.5% deaths on placebo to 12.5% deaths on eplerenone. Cardiovascular mortality was reduced 24% by eplerenone from 13.5% cardiovascular deaths on placebo to 10.8% cardiovascular deaths on eplerenone. A serum potassium greater than 5.5 mEq/L developed in 11.8% of patients treated with eplerenone *versus* 7.2% treated with placebo.¹² In the EMPHASIS-HF trial, in patients with an estimated glomerular filtration rate greater than 30 ml/min/1.73 m² and a serum potassium below 5.0 mEq/L, use of eplerenone was efficacious and safe when carefully monitored even in patients at high risk for hyperkalemia and/or worsening renal function.¹³ Careful surveillance of serum potassium and cautious use of aldosterone antagonist therapy may help to reduce the incidence of potentially hazardous complications caused by hyperkalemia.¹⁴

Among 5,887 medicare patients, mean age 77.6 years, with HFrEF, 18.2% were treated with aldosterone antagonist therapy at hospital discharge.¹⁵ At 3-year follow-up, all-cause mortality was 49.9% in patients treated with aldosterone antagonist therapy and 51.2% in patients not treated with aldosterone antagonist therapy (*p* not significant). At 3-year follow-up, heart failure re-hospitalization was 38.7% in patients treated with aldosterone antagonist therapy *versus* 44.9% in patients not treated with aldosterone antagonist therapy.¹⁵ There was an increase

in re-hospitalization for hyperkalemia, predominantly within 30 days after hospital discharge.¹⁵

We performed a propensity-score analysis in 1,140 hospitalized medicare patients, mean age 76 years, with HFrEF and an estimated glomerular filtration rate below 45 ml/min/1.73 m².¹⁶ This study showed that these patients treated with spironolactone were more likely to be re-hospitalized at 30 days and at 1 year, but there was no association of spironolactone use with all-cause mortality or re-admission for heart failure.¹⁶

We also performed a propensity-score analysis in 2,443 medicare patients, mean age 72 years, with HFrEF.¹⁷ This study showed that use of spironolactone was associated with a 16% insignificant reduction in 30-day all-cause mortality and with a 26% insignificant reduction in 30-day readmission for heart failure.¹⁷

The American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines recommend with a class I indication the addition of an aldosterone antagonist in selected patients with NYHA class II to IV HFrEF who can be carefully monitored for preserved renal function and normal serum potassium concentration.¹⁸ Patients treated with an aldosterone antagonist should have a serum creatinine 2.5 mg/dL or lower in men and 2.0 mg/dL or lower in women, and the serum potassium should be less than 5.0 mEq/L.¹⁸

HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

The prevalence of heart failure with a preserved LVEF (HFpEF) increases with age, is higher in older women than in older men, and is present in approximately 50% of patients with heart failure.^{19,20} By reducing cardiac fibrosis, aldosterone antagonists have the potential to be efficacious in treating patients with HFpEF. Spironolactone improved myocardial function measured by quantitative echocardiographic techniques in 30 hypertensive patients with HFpEF randomized to spironolactone versus double-blind placebo.²¹ In a randomized, double-blind, placebo-controlled trial of 44 patients with HFpEF, eplerenone did not improve at 6 months 6-minute walk distance but did improve markers of collagen turnover and diastolic function.²²

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial was a randomized, double-blind, placebo-controlled trial which randomized 3,445 patients with symptomatic HFpEF to receive either spironolactone 15 mg to 45 mg daily or placebo.^{23,24} The mean dose of spironolactone used was 25.0 mg per day. Of these patients, 1,767 patients were from the United States, Canada, Brazil, and Argentina, and 1,678 patients were from Russia and Georgia. The baseline characteristics were significantly different between the Americas group and the Russia and Georgia group. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for treat-

ment of heart failure. The mean follow-up was 3.3 years.

Spironolactone insignificantly reduced the primary outcome by 11% from 20.4% of patients treated with placebo to 18.6% of patients randomized to spironolactone.²³ Of the primary outcome components, only hospitalization for heart failure was significantly lower by 17% in patients treated with spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels, increased hyperkalemia (18.7% for spironolactone versus 9.1% for placebo), and reduced hypokalemia. There were no differences between spironolactone and placebo in the incidence of serious adverse events.²³

In the Americas group, compared with placebo, spironolactone decreased the primary outcome 18% from 12.6% to 10.4%, decreased cardiovascular mortality 26% from 14.4% to 10.8%, decreased hospitalization for heart failure 18% from 24.5% to 20.8%, decreased recurrent heart failure 25% from 438 events to 361 events, insignificantly decreased all-cause mortality 17% from 23.5% to 20.1%, had similar incidences of all-cause hospitalization, myocardial infarction, and stroke, had a 60% increased incidence of doubling of serum creatinine from 11.6% to 17.8%, had a similar incidence of serum creatinine ≥ 3.0 mg/dL, increased hyperkalemia (≥ 5.5 mmol/L) 3.46 times from 8.9% to 25.2%, and reduced hypokalemia (serum potassium < 3.5 mmol/L) 49% from 26.2% to 15.2%.²⁴

In the Russia and Georgia group, all of these outcomes were similar for patients treated with spironolactone or placebo.²⁴ These marked regional differences suggest that clinical diagnostic criteria were not uniformly interpreted or applied in the Russia and Georgia group. The event rates of those enrolled from the Americas are reflective of other clinical trial populations with symptomatic HFpEF.²³⁻²⁶

CONCLUSION

It is very disturbing that the patients with HFpEF enrolled in Russia/Georgia in the TOPCAT trial did not demonstrate either the expected morbidity and mortality associated with symptomatic HFpEF or with the pharmacological responses expected from use of spironolactone.²⁴ On the basis of the data reported from the Americas group in the TOPCAT trial,²⁴ this author recommends the use of an aldosterone antagonist in the treatment of patients with HFpEF.

CONFLICTS OF INTEREST

The author has no conflicts of interest.

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