Position Statement on
ALDOSTERONE ANTAGONIST THERAPY IN CHRONIC HEART FAILURE

Over 8,000 patients have been studied in two well-designed placebo-controlled outcome-driven clinical trials to evaluate the efficacy of aldosterone antagonism in prolonging life and reducing cardiovascular morbidity in patients with clinical heart failure and/or systolic dysfunction.[1-2] Minor pharmacologic differences exist between the two aldosterone antagonists that have been studied in this settings, spironolactone and eplerenone. Spironolactone's elimination half-life is significantly longer than that of eplerenone, and eplerenone has been shown to preferentially antagonize the aldosterone receptors over other steroid receptors. Although definitive comparative data do not exist for spironolactone and eplerenone, these agents at this time should be considered to likely have comparable efficacy.

Based on the results of the available evidence, we advocate the following:

1. Aldosterone antagonist therapy should be added to standard therapy for patients with NYHA Class IIIb – IV clinical ischemic or non-ischemic heart failure.
2. Following myocardial infarction, aldosterone antagonist therapy should be considered for patients with left ventricular systolic dysfunction or clinical heart failure.
3. Data are not available regarding aldosterone antagonist therapy in patients with mild to moderate non-ischemic heart failure. In these patients, the role of spironolactone or eplerenone has not been established.
4. When initiating aldosterone antagonist therapy, caution should be exercised in patients with renal dysfunction, a propensity to develop renal dysfunction, or an elevated baseline serum potassium; these patients should be frequently evaluated.
5. Spironolactone should be regarded as the aldosterone antagonist of choice. Eplerenone may be considered for use in patients who fail spironolactone (e.g., painful gynecomastia).

Clinical Trials Supporting the Use of Aldosterone Antagonists in Chronic Heart Failure

- Randomized Aldactone Evaluation Study (RALES)
- Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)

Randomized Aldactone Evaluation Study (RALES)[1]

Objective: RALES was designed to evaluate the effect of spironolactone on mortality in patients on standard therapy who had severe heart failure as a result of systolic left ventricular dysfunction.

Methods: 1663 patients with current NYHA Class III or IV heart failure, a history of Class IV heart failure in the previous six months, and a left ventricular ejection fraction $\leq$ 35% were randomized in a double-blind fashion to receive either spironolactone (25 mg po qd, with possible uptitration to 50 mg po qd) or placebo. Background therapy consisted of diuretics (100%), ACE inhibitors (95% in the spironolactone group and 94% in the placebo group), beta-blockers (11% in the spironolactone group and 10% in the placebo group), and digitalis (75% in the spironolactone group and 72% in the placebo group). Patients were excluded for serum creatinine > 2.5 mg/dL or serum potassium > 5.0 mEq/L. Mean follow-up was 24 months.

Results:

- RALES was terminated early by the data and safety monitoring board on the basis of spironolactone's effect on death from all causes.
- The majority of patients in RALES were NYHA Class III (72% in the spironolactone group and 69% in the placebo group). 27% of the spironolactone group and 31% of the placebo group were NYHA Class IV. Four and three patients, respectively, in the spironolactone and placebo groups were NYHA Class II.
- At the end of the study, the mean daily dose of spironolactone achieved was 26 mg.
- Spironolactone showed a 30% reduction in all-cause mortality (46% in the placebo group and 35% in the spironolactone group, $p < 0.001$), a 36% reduction in death from progressive heart failure ($p < 0.001$), a 29% reduction in sudden cardiac death ($p = 0.02$), and a 35% reduction in hospitalization for heart failure ($p < 0.0001$).
- The use of spironolactone was associated with a 1% absolute increase in serious hyperkalemia ($K \geq 6.0$ mEq/L).

Conclusions: The addition of spironolactone to standard therapy for patients with severe heart failure significantly reduces the risks of morbidity and mortality.

Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[2]

Objective: EPHESUS was designed to evaluate the effect of eplerenone on morbidity and mortality in patients with left ventricular systolic dysfunction and heart failure following acute myocardial infarction.

Methods: 6642 patients 3-14 days following acute myocardial infarction, left ventricular ejection fraction $\leq$ 40%, and evidence of heart failure (except patients with diabetes mellitus, who were only required to have systolic dysfunction) were randomized to receive either eplerenone (25 mg po qd for one month, uptitrated to 50 mg po qd in the absence of hyperkalemia) or a matching placebo. Concominant therapy consisted of an ACE inhibitor or angiotensin receptor antagonist (86% in the eplerenone group and 87% in the placebo group), beta-blockers (75%), diuretics (60% in the eplerenone group and 61% in the placebo group), aspirin (88% in the eplerenone group and 89% in the placebo group), and an HMG-CoA reductase inhibitor (47%). Patients were excluded for a serum creatinine $\geq$ 2.5 mg/dL or a serum potassium $\geq$ 5.0 mEq/L. Study medication was initiated at a mean of 7.3 days following myocardial infarction. The mean follow-up was 16 months.

Results:

- The mean LVEF in both groups was 33%.
- The mean daily eplerenone dose achieved was 43 mg.
- The primarily endpoint of overall mortality was 14.4% in the eplerenone group and 16.7% in the placebo group, a 15% reduction in total mortality (relative risk 0.85, p = 0.008).
- Treatment was eplerenone was associated with a 17% reduction in cardiovascular mortality (12.3% in the eplerenone group and 14.6% in the placebo group, relative risk 0.83, p = 0.005).
- Eplerenone therapy was also associated with a 23% reduction in heart failure hospitalizations (relative risk 0.77, p = 0.002).

Conclusions: Eplerenone therapy in patients with left ventricular systolic dysfunction following myocardial infarction reduces morbidity and mortality.

Evidence table

Clinical trial	Patients	Exclusion	Intervention	Mean Follow-up	NYHA Class	Overall Mortality
RALES (1999)[1]	NYHA Class III or IV LVEF ≤ 35% n = 1663	SCr > 2.5 mg/dL K > 5.0 mEq/L	Spironolactone 25-50 mg po qd	24 months	II, 0.4-0.5% III, 69-72% IV, 27-31%	Placebo, 46% Spironolactone, 35% p < 0.001
EPHESUS (2003)[2]	LVEF ≤ 40% Post-AMI n = 6642	SCr ≥ 2.5 mg/dL K ≥ 5.0 mEq/L	Eplerenone 25-50 mg po qd	16 months	N/R	Placebo, 16.7% Eplerenone, 14.4% p = 0.008

AMI, acute myocardial infarction; K, serum potassium; LVEF, left ventricular ejection fraction; N/R, not reported; NYHA, New York Heart Association; SCr, serum creatinine

References

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-717.
2. Pitt B, Remme W, Zannad F, et al, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-1321.