Randomized, Double Blind, Multicenter, Placebo-Controlled Study Evaluating the Effect of Aldosterone Antagonism with Eplerenone on Ventricular Remodeling in Patients with Mild-to-Moderate Heart Failure and Left Ventricular Systolic Dysfunction

James E. Udelson MD, Arthur M. Feldman MD PhD, Barry Greenberg MD, Bertram Pitt MD, Robin Mukherjee PhD, Henry A. Solomon MD, and Marvin A. Konstam MD

From Tufts Medical Center, Boston, MA (JEU, MAK); Jefferson Medical College, Philadelphia, PA (AMF); University of California San Diego Medical Center, San Diego, CA (BG); University of Michigan School of Medicine, Ann Arbor, MI (BP); Pfizer Inc, New York, NY (RM, HAS)

Correspondence:
James E. Udelson, MD
Tufts Medical Center
750 Washington Street, Box 70
Boston, MA 02111
Phone: 617 636-8066
Fax: 617 636-5913
E-mail: JUdelson@tuftsmedicalcenter.org
ABSTRACT

Background: Aldosterone antagonism has been studied in patients with advanced heart failure (HF), and also in patients with post-MI left ventricular (LV) dysfunction with HF symptoms. Few data are available on effects of aldosterone antagonism in patients with mild-to-moderate HF.

Methods and Results: In a multicenter, randomized, double blind, placebo-controlled study in patients with mild-to-moderate heart failure and LV systolic dysfunction, patients with NYHA class II/III HF and LV ejection fraction (EF) ≤ 35% were randomized to receive eplerenone 50 mg/day vs placebo in addition to contemporary background therapy. Quantitative radionuclide ventriculograms to assess LV volumes and EF were performed at baseline, again after 9 months of double-blind treatment, and were analyzed in a central core lab, blinded to treatment. The primary efficacy analysis was the between group comparison of the change in LV end-diastolic volume index (EDVi). Secondary analyses examined changes in LV end-systolic volume index (ESVi) and EF, as well as markers of collagen turnover. Of the total 226 patients enrolled, 117 were randomized to receive eplerenone and 109 to receive placebo. There was high use of contemporary background therapy at baseline, with >90% use of ACE inhibitors and/or angiotensin receptor blockers, and > 90% use of beta-blockers. Over 36 weeks of treatment there was no apparent between-group difference in the changes in EDVi or ESVi. There was a reduction in the collagen turnover marker pro-collagen type I N-terminal propeptide and plasma B-type natriuretic peptide in the eplerenone group when compared to placebo (p=0.01 and p=0.04 respectively). There was no change in symptom status or quality of life measures.

Conclusions: In a clinically stable, well-treated population of patients with mild-to-moderate HF symptoms and LV dysfunction, 36 weeks of treatment of aldosterone antagonism with eplerenone at a dose of 50mg daily had no detectable effect on parameters of LV remodeling.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00082589

Key words: Heart failure, aldosterone, remodeling
Two large trials have demonstrated the benefits of aldosterone blockade on outcomes in subsets of patients with heart failure (HF). In the Randomized Aldactone Evaluation Study (RALES), spironolactone improved survival in patients with a history of advanced HF. [1] More recently, the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that aldosterone blockade with eplerenone, when used with standard heart failure therapy that usually included angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARBs) and beta-blockers (BB), improved survival and reduced heart failure hospitalizations in patients with LVSD (EF ≤40%) and clinical evidence of HF or diabetes after an acute MI. [2]

Several potential mechanisms have been suggested to explain these benefits. Clinical and translational studies have shown that aldosterone blockade reduces LV remodeling and collagen deposition (fibrosis), improves endothelial function, decreases inflammation and increases myocardial perfusion and capillary density. [3-6] Ventricular remodeling has received attention as an endpoint in studies of new therapeutics for HF, because it is thought to generally correlate with outcomes. Importantly, medications demonstrated to retard or reverse the remodeling process usually improve HF clinical outcomes. [7-9]

The effects of aldosterone blockade in patients with LV systolic dysfunction and chronic mild to moderate HF (NYHA functional class II and III), a patient population distinct from that evaluated in RALES and EPHESUS, has not been well studied. Studying this population is important as it represents 60% of the US population with HF and reduced EF, and because they have an annual mortality rate of approximately 10% [10]. The current study is therefore being conducted to evaluate the effects of aldosterone blockade, with eplerenone, on LV remodeling and markers of collagen turnover in patients with LV systolic dysfunction and chronic mild-to-moderate HF.

METHODS
Study Design: This was a randomized, double blind, multicenter, parallel, placebo controlled trial. Eligible patients meeting all inclusion criteria and no exclusion criteria were randomized (1:1) to receive eplerenone or placebo in a double-blind manner. Subjects were assigned at each site to a double-blind treatment arm when they met criteria for randomization. They received their allocated and blinded treatment according to a computer-generated randomization schedule prepared by the sponsor prior to the start of the study. The randomization schedule has a block size of four and there was no stratification factor for the randomization.

Initially after randomization, patients were given 25 mg of eplerenone daily, or matching placebo. After 4 weeks of treatment, the dose of eplerenone was increased to the target dose of 50 mg (two 25 mg tablets daily), or matching placebo. Serum potassium was monitored throughout the study, and if necessary, doses of eplerenone (or placebo) were titrated down. Study drug treatment duration was 36 weeks. Equilibrium gated radionuclide ventriculography (RVG) was performed at baseline prior to randomization, and repeated after 36 weeks of treatment.

Institutional Review Boards at all trial sites approved the study protocol, and all patients signed informed consent to participate.

Study Population: Included were male or non-pregnant female subjects aged 21 years and older with current symptoms consistent with mild to moderate HF (NYHA functional class II and III), who had LV EF of <35% by equilibrium-gated RVG at screening, and were on therapy with an ACEI and/or ARB, and BB (unless documented intolerance) for at least 3 months duration and at a dose that has not been adjusted within the previous 4 weeks. Excluded were patients with current decompensated HF or HF hospitalization or severe HF (NYHA functional class IV) within 6 months of screening, serum potassium >5.5 mEq/L, history of hyperkalemia (K>6.0 mEq/L) with eplerenone or spironolactone, creatinine clearance of <30 mL/min based on the Cockcroft-Gault formula, biventricular pacemaker placed within 6 months of screening, or subjects on or requiring potassium-sparing diuretics or spironolactone.
Radionuclide Ventriculography: The RVG methodology was developed and directed by a central core laboratory as reported in previous studies [8, 11-13], with detailed instructions and quality control procedures reviewed at an Investigator Meeting, and with comments on image quality fed back to sites following transfer of each individual imaging study. Equilibrium-gated RVGs were performed following modified in vivo red blood cell labeling with Tc-99m. A gamma camera was positioned in the modified left-anterior-oblique (LAO) view using a high-resolution parallel-hole collimator, with the degree of obliquity chosen to maximize interventricular and right atrioventricular separation. An approximate 10-degree caudal tilt could be applied to avoid atrial overlap and further enhance chamber separation. The gated LAO scans were acquired for 8 minutes or for a minimum of 5 million counts in a 16-bit word mode, 64x64 matrix, with a 15% window centered at the Tc-99m photopeak. Data acquisition was gated to the patient’s electrocardiogram, with each cardiac cycle divided into 32 frames.

A 5mL heparinized blood sample was drawn midway through the acquisition, placed in a lavender top tube and later pipetted onto a petrie dish, for ventricular volume calculations. Two methods could be used for collecting precise blood samples (8,11,13). In method I, the sample was weighed to calculate the exact volume before counting it on the camera. In method II, an exact volume of blood was pipetted onto a petrie dish and counted on the camera. After completion of the gated scan in the LAO projection, two one-minute static scans were obtained, for the purpose of attenuation correction. This depth acquisition was acquired in a 16-bit word mode, 64x64 matrix, single file containing two frames. The first frame was in the same exact LAO projection as the rest LAO scan and the 2nd frame was in the anterior position.

Activity in the blood sample was counted during a 2 minute, 16-bit word mode, 64x64 matrix acquisition, after the gated and depth images were completed. The single frame static image was acquired using the same gamma camera and collimator as employed for the gated LAO and depth acquisitions. The precise time of the patient and blood sample acquisitions were recorded to permit accurate decay correction. Volumetric measurements and calculation of ejection fraction were performed in a central core.
laboratory, by an experienced technologist and nuclear cardiologist, blinded to treatment group and clinical data. The calculation of volumes was based on previously published methods [8, 11-13].

Markers of Collagen Turnover and Other Biomarkers: Biomarkers including markers of collagen turnover (pro-collagen type I N-terminal propeptide [PINP], pro-collagen type III N-terminal propeptide [PIIINP]), inflammatory markers (CRP, osteopontin), and plasma B-type natriuretic peptide (BNP) were measured at baseline and at Week 36.

Assessment of Symptoms and Quality of Life: New York Heart Association (NYHA) functional class assessment and completion of the Kansas City Cardiomyopathy Questionnaire (KCCQ) were performed at screening visit, at week 1 and at Week 36. The KCCQ is a disease-specific instrument for subjects with heart failure that quantifies the full range of health status as impacted upon by the syndrome of heart failure. [14] The 23-item questionnaire quantifies symptoms (their frequency, severity, and change over time), function (physical and social), and quality of life.

Sample Size Estimation: The sample size estimation was based on the primary efficacy variable EDVi determined by equilibrium-gated RVG. A total of 180 subjects (90 subjects per treatment group) was estimated to provide 90% power to detect a difference of 4.5 mL/m² between the eplerenone and placebo groups in mean change from baseline in EDVi at a 5% level, assuming a standard deviation of the change from baseline of 9.2 mL/m². Based both on prior eplerenone and HF studies, an estimated dropout rate of 10-15% was anticipated. Therefore, approximately 200-210 subjects were required to be randomized.

Statistical Analysis: For continuous parameters, changes from baseline to Week 36 were analyzed using the analysis of covariance (ANCOVA), with change from baseline as the response variable, and baseline value and treatment group as explanatory variables. Departures from model assumptions (e.g., normality) were assessed, and a log transformation or other appropriate procedures were used for the analyses, if necessary.
Comparisons of measurements in the ordinal scale were analyzed using the Cochran-Mantel-Haenszel (CMH) test, based on ridit scores. The primary analysis was performed on the evaluable population, which was defined as the subjects who were on study medication for at least 6 months without major study drug interruption who completed an evaluable follow-up RVG. All other analyses were performed on all subjects who received at least one dose of study drug (safety population). All p-values were two-sided and were compared to a significance level of 0.05.

RESULTS

Study Population
Following screening, a total of 226 patients were randomized into the treatment phase of the study; 117 were randomized to receive eplerenone and 109 to receive placebo, both in addition to standard therapies. The characteristics of the study population at baseline are shown in Table 1. As seen in Table 1 there were no important differences between the treatment groups at baseline. This population of HF patients was well treated, with 96% being treated with ACEi/ARBs, and 95% treated with beta-blocking agents.

Effect of Eplerenone on Ventricular Volumes and Function
The data on the primary endpoint of the study, the effect of eplerenone on EDVi, are shown in Table 2, along with ESVi and EF data. Over 36 weeks of treatment, there was no evidence of an effect of eplerenone compared with placebo on either LV EDVi, LV ESVi, nor on LV EF.

These data reflect the analysis as planned on the evaluable population who completed both the baseline and follow-up imaging studies. In the eplerenone and placebo groups, 11% and 18% of patients were not evaluable respectively (p=0.18). There were no significant differences in baseline characteristics between the evaluable and non-evaluable population samples, with only history of hypertension in the eplerenone group and history of diabetes in the placebo group approaching significance (p=0.08 for both).
Neither blood pressure nor heart rate was significantly affected by eplerenone. Systolic BP change was $0 \pm 16$ mmHg (mean $\pm$ SD) in the eplerenone group and was $0 \pm 16$ mmHg in the placebo group. Diastolic blood pressure change was $-1 \pm 9$ mmHg in the eplerenone group and $0 \pm 11$ mmHg in the placebo group. There was no evidence of a change in mean heart rate between randomized groups ($p=0.79$).

**Effect of Eplerenone on Markers of Collagen Turnover and Other Biomarkers**

The effect of eplerenone on markers of collagen turnover and BNP are shown in Table 3. Over the course of treatment, there was a greater reduction in PINP and BNP ($p$-values = 0.01 and 0.04, respectively) in the eplerenone group when compared to the placebo group. With respect to change from baseline to week 36 in PIIINP, no difference was detected between eplerenone and placebo (Table 3). No differences in changes from baseline were detected in the inflammatory markers CRP and osteopontin during the course of therapy.

**Changes in Symptomatic Status and Quality of Life**

Table 4 displays the distribution of patients across NYHA Classes I, II, and III at baseline and change in NYHA status (worsen, no change, and improve) at Week 36, by randomized group. Based on the Cochran-Mantel Haenszel test there is no evidence ($p=0.27$) of an association between the distribution of patients across the response categories “worsen”, “no change,” and “improve” and the randomized groups, at Week 36. Further, there was no evidence of a difference ($p=0.78$) between the groups in changes on the KCCQ overall summary score.

**Influence of Baseline Variables on Treatment Responses**

Exploratory analyses were performed to identify subgroups that may have shown differential treatment responses, to generate hypotheses for future study. The effect of eplerenone vs. placebo on ventricular volumes in patients grouped by baseline markers of collagen turnover is shown in Figure 1. Among patients whose baseline PINP levels were above the median, there was a reduction in EDVi and ESVi in the eplerenone group compared to placebo across the course of treatment ($p=0.06$ and $p=0.05$ respectively).
contrast, no evidence of changes were detected between either treatment group among patients whose baseline PINP levels were below the median. A similar trend was noted for subgroups above and below the median baseline PIIINP levels.

Changes in Laboratory Parameters and Side Effects of Treatment

Reported adverse events are listed in Table 5. Although the median change in serum potassium during treatment was small (+0.1 mEq/L in the eplerenone group and 0.0 mEq/L in the placebo group), hyperkalemia was reported as an adverse event at some point during the study in 12% of patients during eplerenone therapy and in 6% of patients during placebo therapy.

DISCUSSION

The data from the present study show that in a clinically stable, well-treated population of patients with mild-to-moderate HF symptoms and LV dysfunction, 36 weeks of treatment with eplerenone at a dose of 50mg daily had no detectable effect on parameters of LV remodeling, or function. Treatment with eplerenone was associated with a greater reduction in the collagen turnover marker PINP (though not with PIIINP), and BNP. There were no changes in symptom status or measures of quality of life.

The study was specifically designed to assess the impact of aldosterone antagonism in a population that has not been included in the previous outcomes trials of mineralocorticoid receptor antagonism. RALES studied patients with advanced heart failure, and EPHESUS included patients early post-MI with LV dysfunction who had evidence of HF or diabetes [1,2]. The current trial studied patients between those ends of the spectrum of the continuum of heart failure severity, those with stable mild-to-moderate symptoms, in whom the use of aldosterone antagonism has not been extensively studied.
The primary endpoint data demonstrate no detectable effect of 9 months of aldosterone antagonism on the selected parameter – LV EDVi – compared to placebo. It is of interest that in the placebo group, there was no increase in the group mean LV EDVi over 9 months of follow-up, i.e., no adverse remodeling in this population sample. This finding may be related to the comprehensive background therapy in this group of patients, over 90% of whom were treated with BB as well as an ACE inhibitor and/or an angiotensin receptor blocker. It is also possible that the treatment period of 9 months was too short to see an effect, in that with longer follow-up there could have been more remodeling in the placebo group, or alternatively there could have been more reverse remodeling seen in the active treatment group. In that regard, in the Studies of Left Ventricular Dysfunction Prevention trial of patients with asymptomatic LV dysfunction, differences in remodeling during treatment using enalapril or placebo did not emerge until more than 2 years of therapy [15].

In the absence of an observable effect on chamber remodeling, there was however some evidence of possible treatment effects. There was a reduction in PINP, a marker of collagen turnover, and a directionally similar change in PIIINP, though not significantly so. This finding suggests that aldosterone antagonism in these patients may have favorably impacted the process of interstitial collagen turnover within the myocardium. Moreover, levels of BNP were reduced in the eplerenone group and increased in the placebo group over the course of therapy, suggesting possibly favorable effects on wall stress or other parameters influencing BNP serum levels. All of these data are suggestive of active effects at the myocardial and/or interstitial level, which did not eventuate as observable changes in remodeling at the LV chamber level over the specific time course of therapy in this trial. The effects are small however, and any conclusions must be tempered by the secondary nature of these endpoints.

In exploratory analyses of patient subgroups, interesting findings emerged that could be considered as generating hypotheses for future studies. There was a favorable remodeling effect (greater reduction in EDVi and ESVi) in the eplerenone group compared to placebo in patients whose baseline PINP levels were above the median, and
no effect seen in patients whose baseline PINP levels were below the median. This analysis was consistent with subgroup analysis findings from the RALES study [16], where a more favorable treatment effect of spironolactone on mortality was seen in the subgroup with higher baseline levels of collagen turnover biomarkers compared to those with lower levels. The present data suggest that subsequent studies selecting patients on the basis of markers of collagen turnover may identify a subgroup with a beneficial remodeling effect from aldosterone antagonism.

The existing published data on the use of aldosterone antagonism in stable patients with mild-to-moderate HF have shown inconsistent results, in smaller study populations. In a 40 patient randomized trial of 3 months duration, Berry et al found that spironolactone improved BNP and PIIINP levels compared to placebo, but had unfavorable effects on a quality of life measure and on serum creatinine [17]. Chan and colleagues [18] reported on 51 patients with mild-to-moderate HF, 70% of whom were on beta-blockers. All patients in that study were on ACE inhibitors (dosing not stated) and were randomized to candesartan 8 mg plus spironolactone 25mg daily or to candesartan 8 mg plus placebo. There was a favorable effect of the combined group on remodeling, with no effects on quality of life, and 6 minute walk distance or NYHA class changes. As all patients in both randomization groups were changed from their clinically used ACE inhibitor to candesartan, the incremental benefit associated with aldosterone blockade could not be clearly established or isolated.

Tsutamoto et al studied 37 patients with nonischemic cardiomyopathy and NYHA class II or III symptoms randomized to four months of treatment with spironolactone 25mg daily or placebo [3]. At baseline 73% were on ACEi and 38% on BBs. LV volumes, assessed by transformation of M-mode echo measures using the Teichholz formula, were reduced during treatment with spironolactone, as were PIIINP levels and BNP. Cicoira and colleagues randomized 106 patients with an average NYHA class of 2.2, 69% of whom were on beta-blockers, to treatment with spironolactone up to 50mg daily or placebo for one year, and reported a trend to reduction in LV EDV, with
reduction in LV ESV on active therapy, though baseline imbalances may have come into play [19].

Thus, the effect of aldosterone antagonism for patients with mild-to-moderate HF and LV systolic dysfunction in contemporary practice with currently recommended background therapy has been uncertain. The present study was well powered to detect small changes in volumes, based on data from numerous previous trials using similar methodology, and enrolled a very well treated group of contemporary HF patients. In this setting, there was no evidence of an effect on LV volumetric remodeling parameters with 9 months of eplerenone therapy. It is conceivable that with such high use of background therapies, the temporal pace of the process of remodeling has changed compared to previous studies, and that in this setting, longer observation periods and/or larger sample sizes may be required to demonstrate remodeling effects of a new therapy. Alternatively, it is possible that in the setting of appropriately high use of background therapy, additional neurohormonal antagonism at this stage in the HF syndrome indeed has no incremental effect.

There are limitations to the present analysis. As in all such imaging studies, the data at hand represent an analysis of “completers”, that is, patients who have both baseline and final data for analysis. In this study, there were no apparent differences in baseline characteristics between the evaluable vs the non-evaluable patients, though that comparison is limited by the relatively small numbers in the non-evaluable group. In several previous studies, imputational methods have not appreciably changed the completer analysis results [13]. The generalizability of the present findings to broader populations of HF patients without such high levels of background therapies is uncertain.

Hence, aldosterone antagonism with eplerenone at 50mg daily for 9 months in patients with mild-to-moderate HF and reduced LV EF has no observable effect on parameters of LV remodeling, symptoms or quality of life measures. There was a favorable effect seen on a biomarker reflecting collagen turnover and on BNP. Whether such effects translate into beneficial clinical effects on mortality or morbidity may be
clarified by the ongoing EMPHASIS-HF trial (Effect of Eplerenone Versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects With NYHA Class II Chronic Systolic Heart Failure). [20]. It is of interest that two large randomized trials (RALES and EPHESUS [1,2]) have shown significantly favorable effects of aldosterone antagonism on outcomes, yet in those specific populations there has not been a clearly demonstrable favorable effect of aldosterone antagonism on remodeling. Thus the underlying mechanism(s) of the favorable outcome effect in those population types has yet to be determined. Exploratory subgroup analysis in the current trial suggested a possible favorable effect on remodeling among patients with elevated collagen turnover activity at baseline. These latter results support the concept that future studies should explore targeting such patients.
Appendix:

Sites and Investigators

Dr. Arthur Bleakley Chandler, Cardiovascular Associates of Augusta, Augusta, GA

Dr. Larry Michael Altschul, Dr. Michael Masciello, South Bay Cardiovascular Associates, West Islip, NY

Dr. Pablo A. Guzman, Cardiology Associates of Fort Lauderdale, P.A., Fort Lauderdale, FL

Dr. Detlef Wencker, Dr. Stuart David Katz, Yale University School of Medicine, New Haven, CT

Dr. David Hinchman, Idaho Cardiology Assoc, Boise, ID

Dr. Mark David Nathan, Cardiovascular Consultants Inc, Walnut Creek, CA

Dr. Marvin Kronenberg, Vanderbilt Clinical Trials Center, Nashville, TN

Dr. Eugene S. Chung, The Linder Clinical Trial Center, Cincinnati, OH

Dr. Robert Braastad, Illinois Heart & Lung Associates, S.C, Normal, IL

Dr. Enrique Flores, Georgia Heart Specialists, Covington, GA

Dr. Dwight Stapleton, Guthrie Clinic, Ltd., Sayre, PA

Dr. Mary Norine Walsh, Care Group, Llc, Indianapolis, IN

Dr. Edouard Daher, Dr. Maya E. Guglin, John D. Dingell VA Medical Center, Detroit, MI

Dr. Claire S. Duvernoy, Dr. Peter V. Vaitkevicius, VA Ann Arbor Healthcare System, Ann Arbor, MI

Dr. Steven Goldsmith, Cardiovascular Consultants and Hennepin County Medical Center, Minneapolis, MN

Dr. Terrence Xavier O'Brien, Ralph H. Johnson VAMC, Charleston, SC

Dr. David Gary Wolinsky, Albany Associates in Cardiology, Albany, NY

Dr. Michael Koren, Florida Physicians & Research Associates, Jacksonville, FL
Dr. Thierry H. Lejemtel, Albert Einstein College of Medicine, Division of Cardiology, Bronx, NY

Dr. Frank A. McGrew III, Stern Cardiovascular Center Research Department, Germantown, TN

Dr. Patrick Coleman, Northern California Medical Associates, Santa Rosa, CA

Dr. Donna Mancini, New York Presbyterian Hospital, Columbia Presbyterian Center, New York, NY

Dr. John Schmedtje Jr., Roanoke Heart Institute, Roanoke, VA

Dr. Paul J. Hauptman, St. Louis University, St. Louis, MO

Dr. Gary Hanovich, Dr. Jay Simonson, Cardiovascular Consultants Ltd, Minneapolis, MN

Dr. Thomas Noonan, Blackstone Cardiology Associates, P.C., Pawtucket, RI

Dr. Steven Krueger, BryanLGH Heart Institute, Lincoln, NE

Dr. Daniel J. Lenihan, Dr. Ann Tong, The University of Texas MD Anderson Cancer Center, Houston, TX

Dr. Jonathan Sackner-Bernstein, North Shore University Hospital, Manhasset, NY

Dr. Edward Geltman, Washington University School of Medicine, St. Louis, MO

Dr. Alan Miller, University of Florida Health Science Center, Jacksonville, FL

Dr. Kenneth Taylor, Cardiac Disease Specialists, Atlanta, GA

Dr. Behzad Taghizadeh, Advanced Health Institute, Galax, VA, Mount Airy, NC, and Winston-Salem, NC

Dr. Alan T. Kono, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Dr. Waqas Ghumman, Clarian Congestive Heart Failure Clinic, Indianapolis, IN

Dr. JoAnn Lindenfeld, Univ of Colorado Health Sci Ctr, Denver, CO

Dr. Paul J. Mather, Jefferson Heart Institute, Philadelphia, PA

Dr. Mariell L. Jessup, University of Pennsylvania, Heart Failure / Transplant, Philadelphia, PA
Dr. Nancy K. Sweitzer, University of Wisconsin Hospital & Clinics, Madison, WI

Dr. Denise Hermann, UCSD Medical Center, San Diego, CA

Dr. Michael E. McIvor, Advanced Nuclear Imaging Technology, LLC and Foundation Research, St. Petersburg, FL

Dr. Robert Jay Weiss, Androscoggin Cardiology Associates, Auburn, ME

Dr. Robert Kipperman, Oklahoma Foundation for Cardiovascular Research, Oklahoma City, OK

Dr. Hassan Ibrahim, North Ohio Heart Ctr Sandusky, OH

Dr. Rodolfo Sotolongo, Southeast Texas Cardiology Assoc. II, LLP, Beaumont, TX

Dr. David Joyce , North Ohio Heart Center, Lorain, OH

Dr. Carl John Gessler Jr., Dr. Walter Herbert Haught, Heart Center, Huntsville, AL

Dr. Steven Leigh Grainer, Long Island Cardiovascular Research, PC, Seaford, NY

Dr. John Lualdi, Cardiovascular Consultants, Scarborough, ME

Dr. Ernesto Rivera, Amarillo Heart Clinical Research Inst., Amarillo, TX

Dr. Jeffrey West, Cardiovascular Consultants Medical Group, Castro Valley, CA

Source of funding: This trial was funded by Pfizer Inc, and thus all investigators and/or their institutions received research funding from Pfizer.

Conflict of Interest Disclosure: Drs. Udelson, Feldman, Greenberg, Pitt and Konstam received compensation for Steering Committee activities. Drs. Mukherjee and Solomon were employees of Pfizer at the time the study was performed.
REFERENCES


20) Effect of Eplerenone Versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects With NYHA Class II Chronic Systolic Heart Failure. ClinicalTrials.gov identifier NCT00232180.


Accessed September 3, 2009
Table 1 - Baseline Characteristics of the Population Sample

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone n=117</th>
<th>Placebo n=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male (%)</td>
<td>98 (83.8%)</td>
<td>91 (83.5%)</td>
</tr>
<tr>
<td>Age (SD) in years</td>
<td>63.3 (12.2)</td>
<td>62.0 (12.9)</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>81.2%</td>
<td>85.3%</td>
</tr>
<tr>
<td>Weight in kg (SD)</td>
<td>90.5 (21.3)</td>
<td>89.3 (20.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76 (65.0%)</td>
<td>61 (56.0%)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>47 (40.2%)</td>
<td>40 (36.7)</td>
</tr>
<tr>
<td>HF Ischemic Etiology (%)</td>
<td>60%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Background Medications

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone n=117</th>
<th>Placebo n=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor and/or ARB (%)</td>
<td>86+25 (94.9%)</td>
<td>86+21 (98.2%)</td>
</tr>
<tr>
<td>Beta Blocker (%)</td>
<td>113 (96.6%)</td>
<td>102 (93.6%)</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>83 (70.9%)</td>
<td>76 (69.7%)</td>
</tr>
<tr>
<td>NYHA class 2/3 (%)</td>
<td>116 (91.9%)</td>
<td>109 (100%)</td>
</tr>
<tr>
<td>LVEF (%) [mean (se)]</td>
<td>26.2 (0.6)</td>
<td>27.0 (0.6)</td>
</tr>
</tbody>
</table>

Serum creatinine (mg/dL) (median) | 1.2 | 1.2
Serum potassium (mEq/L) (median) | 4.3 | 4.3

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; HF: heart failure
Table 2 – Baseline and Changes Over 36 Weeks in Left Ventricular Volumes and Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean±SE)</th>
<th>Δ Week 36 (Mean±SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eplerenone (n=117)</td>
<td>Placebo (n=109)</td>
<td></td>
</tr>
<tr>
<td>LV EDVI (mL/m²)</td>
<td>167.0 (4.41)</td>
<td>161.7 (4.49)</td>
<td>-3.7 (1.76)</td>
</tr>
<tr>
<td></td>
<td>Eplerenone (n=104)</td>
<td>Placebo (n=89)</td>
<td></td>
</tr>
<tr>
<td>LV ESVI (mL/m²)</td>
<td>124.3 (3.94)</td>
<td>119.9 (3.97)</td>
<td>-5.1 (1.47)</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>26.2 (0.64)</td>
<td>27.0 (0.56)</td>
<td>1.8 (0.37)</td>
</tr>
</tbody>
</table>

LV EDVI: left ventricular end-diastolic volume indexed to body surface area; LV ESVI: left ventricular end-systolic volume indexed to body surface area; LV EF: left ventricular ejection fraction. Changes are compared to baseline.

¹ Comparison versus baseline. P-value is associated with the change from baseline to week 36 EDVi in the ANCOVA model with treatment group, and baseline value as the only factors.
Table 3 – Baseline and Changes Over 36 Weeks in Markers of Collagen Turnover and BNP

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean±SE)</th>
<th>Δ Week 36 (Mean±SE)</th>
<th>p †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eplerenone</td>
<td>Placebo</td>
<td>Eplerenone</td>
</tr>
<tr>
<td>PIIINP (ug/L)</td>
<td>4.9 (0.16)</td>
<td>4.5 (0.15)</td>
<td>-0.5 (0.17)</td>
</tr>
<tr>
<td>PINP (ug/L)</td>
<td>42.7 (2.31)</td>
<td>44.0 (1.66)</td>
<td>-6.7 (2.04)</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>248.3 (34.65)</td>
<td>197.5 (20.79)</td>
<td>-73.7 (31.55)</td>
</tr>
</tbody>
</table>

† - P-value is associated with the change from baseline to week 36 EDVi in the ANCOVA model with treatment group, and baseline value as the only factors.
Table 4 - Changes in NYHA class from Baseline to Week 36

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N = 117)</th>
<th>Placebo (N = 109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1 (0.9%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>79 (67.5%)</td>
<td>87 (79.8%)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>37 (31.6%)</td>
<td>22 (20.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Change from baseline to Wk 36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsen</td>
<td>10 (8.7%)</td>
<td>7 (6.9%)</td>
<td>0.27</td>
</tr>
<tr>
<td>No change</td>
<td>73 (63.5%)</td>
<td>76 (74.5%)</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>32 (27.8%)</td>
<td>19 (18.6%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Most Frequently Reported Adverse Events in Each Treatment Group, Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N = 117)</th>
<th>Placebo (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n, %</td>
<td>n, %</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (13.7)</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>14 (12.0)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>11 (9.4)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11 (9.4)</td>
<td>15 (13.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (8.5)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (7.7)</td>
<td>22 (20.2)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>9 (7.7)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9 (7.7)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (6.8)</td>
<td>10 (9.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (5.1)</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (5.1)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>6 (5.1)</td>
<td>13 (11.9)</td>
</tr>
</tbody>
</table>
Figure 1. Changes from baseline to Week 36 in (A) left ventricular end-diastolic volume and (B) left ventricular end-systolic volume index as stratified by baseline level of the collagen biomarker PINP.
LVEDVi, left ventricular end-diastolic volume index
B

$P = 0.05$

$P = 0.73$

Change in LVEDVi, left ventricular end-systolic volume index
Randomized, Double Blind, Multicenter, Placebo-Controlled Study Evaluating the Effect of Aldosterone Antagonism with Eplerenone on Ventricular Remodeling in Patients with Mild-to-Moderate Heart Failure and Left Ventricular Systolic Dysfunction

James E. Udelson, Arthur M. Feldman, Barry Greenberg, Bertram Pitt, Robin Mukherjee, Henry A. Solomon and Marvin A. Konstam

Circ Heart Fail. published online March 18, 2010;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2010/03/18/CIRCHEARTFAILURE.109.906909