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

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Background—Aldosterone antagonism has been studied in patients with advanced heart failure (HF) and also in patients with post-myocardial infarction and 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 HF and LV systolic dysfunction, patients with New York Heart Association class II/III HF and LV ejection fraction (EF) ≤35% were randomly assigned to receive eplerenone 50 mg/d versus placebo in addition to contemporary background therapy. Quantitative radionuclide ventriculograms to assess LV volumes and ejection fraction were performed at baseline and again after 9 months of double-blind treatment and were analyzed in a central core laboratory, blinded to treatment. The primary efficacy analysis was the between-group comparison of the change in LV end-diastolic volume index. Secondary analyses examined changes in LV end-systolic volume index and ejection fraction as well as markers of collagen turnover. Of the total 226 patients enrolled, 117 were randomly assigned to receive eplerenone and 109 to receive placebo. There was high use of contemporary background therapy at baseline, with >90% use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers and >90% use of β-blockers. Over 36 weeks of treatment, there was no apparent between-group difference in the changes in end-diastolic volume index or end-systolic volume index. There was a reduction in the collagen turnover marker procollagen type I N-terminal propeptide and plasma B-type natriuretic peptide in the eplerenone group compared with 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 50 mg daily had no detectable effect on parameters of LV remodeling.

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

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Key Words: heart failure ■ pharmacology ■ 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. More recently, the Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that aldosterone blockade with eplerenone, when used with standard HF therapy that usually included angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers and β-blockers (BBs), improved survival and reduced HF hospitalizations in patients with left ventricular (LV) systolic dysfunction (ejection fraction [EF] ≤40%) and clinical evidence of HF or diabetes after an acute myocardial infarction.

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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 end point 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 (New York Heart Association [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 because it represents 60% of the US population with HF and reduced EF and because they have an annual mortality rate of ~10%.10 This 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 before the start of the study. The randomization schedule has a block size of 4, 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 before randomization and repeated after 36 weeks of treatment.

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

Study Population

Included were male or nonpregnant female subjects aged 21 years and older with current symptoms consistent with mild-to-moderate HF (NYHA functional class II and III) who had LVEF of >35% by equilibrium-gated RVG at screening and were on therapy with an ACEI and/or an angiotensin receptor blocker 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.

RVG

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 after 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 ativoventricular separation. An ~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, 64×64 matrix, with a 15% window centered at the Tc-99m photopeak. Data acquisition was gated to the patient’s ECG, with each cardiac cycle divided into 32 frames.

A 5 mL heparinized blood sample was drawn midway through the acquisition, placed in a lavender top tube and later pipetted onto a Petri 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 Petri dish and counted on the camera. After completion of the gated scan in the LAO projection, two 1-minute static scans were obtained for the purpose of attenuation correction. This depth acquisition was acquired in a 16-bit word mode, 64×64 matrix, single file containing 2 frames. The first frame was in the same LAO projection as the rest LAO scan, and the second frame was in the anterior position.

Activity in the blood sample was counted during a 2-minute, 16-bit word mode, 64×64 matrix acquisition, after the gated and depth images were completed. The single frame static image was acquired by using the same gamma camera and collimator as used 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 EF 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 (procollagen type I N-terminal propeptide [PINP] and procollagen type III N-terminal propeptide [PIINP]), inflammatory markers (C-reactive protein and osteopontin), and plasma B-type natriuretic peptide (BNP) were measured at baseline and at Week 36.

Assessment of Symptoms and Quality of Life

NYHA functional class assessment and completion of the Kansas City Cardiomyopathy Questionnaire were performed at screening visit, at week 1, and at Week 36. The Kansas City Cardiomyopathy Questionnaire is a disease-specific instrument for subjects with HF that quantifies the full range of health status as impacted on by the syndrome of HF.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 end-diastolic volume index (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 SD of the change from baseline of 9.2 mL/m². Based on both previous eplerenone and HF studies, an estimated dropout rate of 10% to 15% was anticipated. Therefore, ~200 to 210 subjects were required to be randomized.
Table 1. Baseline Characteristics of the Population Sample

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (n=117)</th>
<th>Placebo (n=109)</th>
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<tbody>
<tr>
<td>Gender (male)</td>
<td>98 (83.8)</td>
<td>91 (83.5)</td>
</tr>
<tr>
<td>Age (SD), y</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>
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<tr>
<td>Weight (SD), kg</td>
<td>90.5 (21.3)</td>
<td>89.3 (20.6)</td>
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<tr>
<td>Hypertension</td>
<td>76 (65.0)</td>
<td>61 (56.0)</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>47 (40.2)</td>
<td>40 (36.7)</td>
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<tr>
<td>HF due to ischemic cause, %</td>
<td>60 (51.7)</td>
<td>60 (55.0)</td>
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<th>Background medications</th>
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<tr>
<td>ACEI and/or ARB</td>
<td>86 (92.5)</td>
<td>86 (98.2)</td>
</tr>
<tr>
<td>BB</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 II/III</td>
<td>116 (99)</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>
<tr>
<td>Serum creatinine (median), mg/dL</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Serum potassium (median), mEq/L</td>
<td>4.3</td>
<td>4.3</td>
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Values are presented as n (%) unless otherwise indicated. ARB indicates angiotensin receptor blocker.

Table 2. Baseline and Changes Over 36 Weeks in LV Volumes and Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean±SE)</th>
<th>Δ Week 36 (Mean±SE)</th>
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<tr>
<td></td>
<td>Eplerenone (n=117)</td>
<td>Placebo (n=109)</td>
</tr>
<tr>
<td></td>
<td>Eplerenone (n=104)</td>
<td>Placebo (n=89)</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>167.0 (4.41)</td>
<td>161.7 (4.49)</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>124.3 (3.94)</td>
<td>119.9 (3.97)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26.2 (0.64)</td>
<td>27.0 (0.56)</td>
</tr>
<tr>
<td>P*</td>
<td>0.48</td>
<td>0.35</td>
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</tbody>
</table>
| Changes are compared to baseline. LVEDVi indicates LVEDVi indexed to body surface area; LVESVi, LVESVi indexed to body surface area.

*Comparison vs 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.

Results

Study Population

Following screening, a total of 226 patients were randomly assigned in the treatment phase of the study; 117 were randomly assigned 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 patients with HF was well treated, with 96% being treated with ACEIs/angiotensin receptor blockers and 95% treated with β-blocking agents.

Effect of Eplerenone on Ventricular Volumes and Function

The data on the primary end point of the study, the effect of eplerenone on EDVi, are shown in Table 2, along with end-systolic volume index (ESVi) and EF data. Over 36 weeks of treatment, there was no evidence of an effect of eplerenone compared with placebo on LVEDVi, LVESVi, or LVEF.

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 evaluated respectively (P=0.18). There were no significant differences in baseline characteristics between the evaluable and nonevaluable 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±16 mm Hg (mean±SD) in the eplerenone group and 0±16 mm Hg in the placebo group. Diastolic blood pressure change was −1±6 mm Hg in the eplerenone group and 0±11 mm Hg 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. During 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 with the placebo group. With respect to change from baseline to week 36 in PIINP, 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
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 versus placebo on ventricular volumes in patients grouped by baseline markers of collagen turnover is shown in the Figure. Among patients whose baseline PINP levels were above the median, there was a reduction in EDVi and ESVi in the eplerenone group compared with placebo across the course of treatment ($P_{\text{H11005}=0.06}$ and $P_{\text{H11005}=0.05}$, respectively). In contrast, no evidence of changes was 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 this 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 50 mg 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 effect 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 HF, and EPHESUS included patients with early post-myocardial infarction with LV dysfunction who had evidence of HF or diabetes. The current trial studied those patients between ends of the spectrum of the continuum of HF severity and those with stable mild-to-moderate symptoms, in whom the use of aldosterone antagonism has not been extensively studied.

The primary end point data demonstrate no detectable effect of 9 months of aldosterone antagonism on the selected parameter LVEDVi compared with placebo. It is of interest

<table>
<thead>
<tr>
<th>Eplerenone (N=117)</th>
<th>Placebo (N=109)</th>
<th>$P$</th>
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<tbody>
<tr>
<td>NYHA baseline</td>
<td></td>
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</tr>
<tr>
<td>Class I</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Class II</td>
<td>79 (67.5)</td>
<td>87 (79.8)</td>
</tr>
<tr>
<td>Class III</td>
<td>37 (31.6)</td>
<td>22 (20.2)</td>
</tr>
<tr>
<td>Change from baseline to wk 36</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Worsen</td>
<td>10 (8.7)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>No change</td>
<td>73 (63.5)</td>
<td>76 (74.5)</td>
</tr>
<tr>
<td>Improved</td>
<td>32 (27.8)</td>
<td>19 (18.6)</td>
</tr>
</tbody>
</table>

Values are presented as n (%).
that in the placebo group, there was no increase in the group mean LVEDVi over 9 months of follow-up, ie, 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 and ACEI 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 this 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 >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 effected 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 during 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 during the specific time course of therapy in this trial. However, the effects are small, and any conclusions must be tempered by the secondary nature of these end points.

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 with placebo in patients whose baseline PINP levels were above the median, and no effect was 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 with 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 al17 found that spironolactone improved BNP and PIIINP levels compared with placebo but had unfavorable effects on a quality-of-life measure and on serum creatinine. Chan et al18 reported on 51 patients with mild-to-moderate HF, 70% of whom were on BBs. All patients in that study were on ACEIs (dosing not stated) and were randomly assigned to candesartan 8 mg and spironolactone 25 mg daily or to candesartan 8 mg and 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 ACEI to candesartan, the incremental benefit associated with aldosterone blockade could not be clearly established or isolated.

Tsutamoto et al3 studied 37 patients with nonischemic cardiomyopathy and NYHA class II or III symptoms randomly assigned to 4 months of treatment with spironolactone 25 mg daily or placebo. 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 et al19 randomly assigned 106 patients with an average NYHA class of 2.2, 69% of whom were on BBs, to treatment with spironolactone up to 50 mg daily or placebo for 1 year and reported a trend to reduction in LVEDV, with reduction in LVESV on active therapy, although baseline imbalances may have come into play.

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. This 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 patients with contemporary HF. 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 with 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 neurohumoral 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,” ie, patients who have both baseline and final data for analysis. In this study, there were no apparent differences in baseline characteristics between the evaluable versus the nonevaluable patients, although that comparison is limited by the relatively small numbers in the nonevaluable 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 patients with HF without such high levels of background therapies is uncertain.

Hence, aldosterone antagonism with eplerenone at 50 mg daily for 9 months in patients with mild-to-moderate HF and reduced LVEF 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 2 large randomized trials (RALES and EPHESUS1,2) 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 mechanisms of the favorable outcome effect in those population types have 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
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References


CLINICAL PERSPECTIVE

Few data are available on effects of aldosterone antagonism in patients with mild-to-moderate heart failure (HF). In this multicenter, randomized, double-blind, placebo-controlled study, patients with mild-to-moderate heart failure and LV systolic dysfunction were randomly assigned to receive eplerenone 50 mg/d versus placebo in addition to contemporary background therapy. The primary efficacy analysis was the between-group comparison of the change in LV end-diastolic volume index by quantitative radionuclide ventriculograms. Over 36 weeks of treatment there was no apparent between-group difference in the changes in end-diastolic volume index. There was a reduction in the collagen turnover volume index by quantitative radionuclide ventriculograms. Over 36 weeks of treatment there was no apparent difference in the changes in end-diastolic volume index. There was a reduction in the collagen turnover volume index by quantitative radionuclide ventriculograms. Over 36 weeks of treatment there was no apparent difference in the changes in end-diastolic 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

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