Effects of Eplerenone, Enalapril, and Eplerenone/Enalapril in Patients With Essential Hypertension and Left Ventricular Hypertrophy

The 4E–Left Ventricular Hypertrophy Study

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Background—Elevated renin-angiotensin-aldosterone system activity correlates with left ventricular hypertrophy (LVH) and cardiovascular risk, but the relative contributions of angiotensin II and aldosterone remain unclear. This study compared LVH regression during treatment with the selective aldosterone blocker eplerenone, enalapril, and their combination in patients with hypertension.

Methods and Results—A 9-month, double-blind, randomized study was performed in 202 patients with LVH and hypertension who received eplerenone 200 mg daily, enalapril 40 mg daily, or eplerenone 200 mg and enalapril 10 mg daily. At week 8, hydrochlorothiazide 12.5 to 25 mg and/or amlodipine 10 mg was added if diastolic blood pressure was >90 mm Hg. Change in left ventricular (LV) mass as assessed by MRI was the primary end point. Change in blood pressure, renin-angiotensin-aldosterone system hormones, albuminuria, and safety were also assessed. Eplerenone significantly reduced LV mass from baseline (14.5 ± 3.36 g; n = 50) similarly to enalapril (19.7 ± 3.20 g; n = 54; P = 0.258), but eplerenone/enalapril (27.2 ± 3.39 g; n = 49) was more effective than eplerenone alone (P = 0.007). All treatments reduced systolic blood pressure and diastolic blood pressure from baseline (eplerenone, 23.8 and 11.9 mm Hg; enalapril, 24.7 and 13.4 mm Hg; and eplerenone/enalapril, 28.7 and 14.4 mm Hg, P = 0.048, in systolic blood pressure compared with eplerenone alone). Cough was more common with enalapril than with eplerenone (P = 0.033), and elevated potassium was more common with eplerenone.

Conclusions—Eplerenone was as effective as enalapril in LVH regression and blood pressure control. The combination of eplerenone and enalapril was more effective in reducing LV mass and systolic blood pressure than eplerenone alone. (Circulation. 2003;108:1831-1838.)

Key Words: hypertrophy • ventricles • blood pressure • hypertension

Left ventricular hypertrophy (LVH) confers an excess risk of cardiovascular and cerebrovascular events in patients with essential hypertension, which is independent of blood pressure (BP).1–3 Consequently, reversal of LVH is an important goal of antihypertensive therapy. Recently, the Losartan Intervention For Endpoint (LIFE) study showed that reduction in left ventricular (LV) mass by angiotensin II (Ang II) blockade was independent of BP reduction, indicating that inhibition of the renin-angiotensin-aldosterone system (RAAS) has added benefits beyond BP control.4 Inhibiting Ang II also suppresses aldosterone production. This suppression reverses with time in response to non–Ang II regulators of aldosterone production, such as serum potassium.5 Animal studies suggest that aldosterone can have an adverse effect on the heart, independent of Ang II,6 including a vascular inflammatory response, myocyte necrosis, fibrosis, and hypertrophy.7 The primary purpose of this study was to compare LV mass regression by the selective aldosterone blocker eplerenone to enalapril and the combination of eplerenone/enalapril in hypertensive patients with LVH.
Hypertension with echocardiographic evidence of LVH

14-day placebo run-in

EPL 200 mg
e (n = 66)
ENAL 40 mg
e (n = 71)
EPL 200 mg
ENAL 10 mg
e (n = 67)

\( \Delta \) LV mass by MRI
\( \Delta \) SBP/DBP
\( \Delta \) UACR
Safety

Figure 1. Study schematic. *Add-on therapy at week 8 with hydrochlorothiazide 12.5 or 25 mg and/or amlodipine 10 mg in patients with DBP >90 mm Hg or SBP >180 mm Hg. ENAL indicates enalapril; EPL, eplerenone.

Methods

Study Population

Male and nonpregnant female adult subjects were eligible if they had LVH diagnosed by either ECG or echocardiogram, had a history of hypertension (ie, seated diastolic blood pressure [DBP] <110 mm Hg and seated systolic blood pressure [SBP] ≤180 mm Hg if presently treated) and antihypertensive medications or DBP ≥90 mm Hg and SBP ≥140 to 180 mm Hg if not presently treated, and were predominantly in sinus rhythm. LVH was documented by ECG (Sokolow-Lyon voltage criteria [≥35 mm]) or echocardiogram (Devereux criteria [LV mass index ≥134 g/m² for men and ≥110 g/m² for women]) or indexed according to height, weight, or height raised to the power of 2.7 (LV mass/height ≥126 g/m² for men and ≥102 g/m² for women, LV mass/height² ≥49.2 g/m² for men and ≥46.7 g/m² for women, or LV mass/body surface area ≥134 g/m² for men and ≥110 g/m² for women).10 The ECG or echocardiogram indicating LVH had to be performed within the 12 months before study entrance in patients who were treated with agents other than ACE inhibitors or angiotensin receptor blockers or 6 months before study entrance in patients taking ACE inhibitors or angiotensin receptor blockers. Before inclusion in the 14-day, single-blind, placebo run-in period (Figure 1), patients had to have an echocardiogram confirming LVH per the criteria described above.

Patients were excluded if any of the following criteria were present: orthostatic hypotension; use of guanethidine, spironolactone, or reserpine in the prior 30 days; serum potassium level <3.0 or >5.0 mEq/L; serum creatinine level >1.5 mg/dl for men and >1.3 mg/dl for women; contraindication to MRI; left ventricular ejection fraction <40% on echocardiogram; New York Heart Association class III to IV congestive heart failure or unstable angina; a history in the prior 6 months of Q-wave myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft; secondary hypertension; contraindication or hypersensitivity to any study medication; type 1 or uncontrolled type 2 diabetes mellitus; acute or chronic hepatic disease; impaired renal function; drug or alcohol abuse problems; terminal illness; or the use of an investigational drug in the prior 30 days. Women were ineligible if they were pregnant.

Study Design

This was a 9-month, placebo run-in, randomized, double-blind, active-controlled, parallel-group study. After gradual withdrawal of antihypertensive medications, patients took placebo for a 14-day, single-blind, run-in period (Figure 1). Patients who were compliant with placebo during the run-in phase, whose DBP was 90 to 114 mm Hg, and whose SBP was 141 to 200 mm Hg underwent a baseline MRI to determine LV mass within 21 days after receipt of the first dose of double-blind study medication.

Patients were then randomly assigned to receive once-daily eplerenone 200-mg tablet plus placebo capsule, enalapril 40-mg capsule plus placebo tablet, or eplerenone 200-mg tablet plus enalapril 10-mg capsule; these doses were reached after a 4-week forced-titration schedule. Attempts were made to normalize BP in all patients in the trial. To do so, patients whose BP remained uncontrolled on study medication (DBP ≥90 mm Hg or SBP >180 mm Hg) at week 8 could be given additional open-label hydrochlorothiazide (HCTZ) 12.5 to 25 mg and/or amlodipine 10 mg.

Discontinuation of study drug was mandatory for treatment failure, which was defined as any of the following: symptomatic hypotension; sustained DBP ≥90 mm Hg or SBP >180 mm Hg on or after week 16; DBP >115 mm Hg or SBP >200 mm Hg at 2 consecutive visits, 3 to 10 days apart, at any time during study participation; and a need to receive antihypertensive medicines not included in the protocol.

Patients were not permitted to take the following medications during the study: antihypertensives or diuretics other than the study medications; medications causing systemic vasodilation or vasoconstriction (eg, sildenafil or theophylline) in the 24 hours before a clinic visit; nitrates other than a stable nitrate dose for stable angina; long-term (>2 weeks) glucocorticoid therapy (thyroid and estrogen hormone replacement were permitted); immunosuppressive or cytotoxic agents; β-blockers or α-blockers for BP regulation; or bronchodilators either daily or acutely on the day of a clinic visit.

For each study site, the ethics committee or institutional review board approved the protocol and informed consent form. Patients provided written informed consent 1 to 2 weeks before entry into the placebo run-in period, before any study procedures were performed or any medication changes occurred.

Cardiac MRI Methods

A common MRI protocol devised by the MRI Core Laboratory used ECG-gated, breath-hold, segmented k-space gradient-echo imaging using 8-mm slice thickness, field of view 30 cm or less, 128×256 matrix, and temporal resolution ≤50 ms. Localizers defined the LV short axis; images were acquired from the left ventricle to the apex of the left ventricle. Studies were immediately forwarded to the MRI Core Laboratory and reviewed for quality and completeness within 24 hours. Image analyses at the Core Laboratory were done in blinded fashion by trained image analysts and overseen by experienced cardiac MRI investigators. Bland-Altman analysis for intraobserver variability showed a bias of 1.3 mg/dl, with 95% limits of agreement −1.6 to 10.54 g. For the posttreatment subset, Bland-Altman intraobserver variability showed a bias of 1.56±0.46 g, with 95% confidence limits −0.14 to 12.26 g (correlation coefficient, 0.994). LV mass was calculated as the product of slice thickness, number of pixels, and absolute pixel size.

Outcome Measures

The primary efficacy measure was change from baseline in LV mass among patients who had a baseline MRI and an end point MRI at month 9 or at the time of study discontinuation (MRI studies were not performed if treatment had been administered for less than 3 months). Secondary efficacy measures included change from baseline in BP, urinary albumin excretion, and RAAS hormones. BP was measured in the seated position with a calibrated sphygmomanometer at all visits, and the mean of 2 measurements taken at least 5 minutes apart was used in the BP analysis. Samples for urinary albumin were collected at weeks 0 and 12 and at months 6 and 9 (or final visit); data were expressed as the urinary albumin:creatinine ratio (UACR). Blood samples for active plasma renin and serum aldosterone levels were drawn before 10:00 AM, after patients had been seated for ≥30 minutes, at weeks 0 and 12 and at months 6 and 9 (or final visit).

Serum potassium levels, concomitant medications, and adverse events were assessed at screening before placebo run in, at clinic visits during the double-blind phase at weeks 0 (baseline), 2, 4, 6, 8, 10, and 12, and then monthly for 9 months. Safety was evaluated by...
A total of 153 patients (eplerenone, n = 50; enalapril, n = 54; eplerenone/enalapril, n = 49) met the criteria for inclusion into the MRI cohort (ie, randomized patients who received double-blind treatment for at least 3 months and who had a baseline MRI and an end point MRI within 21 days after a dose of study medication). There were no significant differences among groups with respect to demographic or baseline characteristics, with the exception of female height (Table 1). Mean MRI LV mass and BP values were similar among groups at baseline. Demographic and baseline characteristics in the total randomized population (n = 64, 71, and 67 for eplerenone, enalapril, and eplerenone/enalapril treatment groups, respectively) were similar (data not shown) to those of MRI patients. Patient disposition is summarized in Table 2.

### Changes in Left Ventricular Mass

Treatment with eplerenone resulted in an adjusted mean change of $-14.5 \pm 3.36$ g in LV mass at month 9 (Figure 2) ($P < 0.001$ versus baseline). Treatment with enalapril resulted in an adjusted mean change of $-19.7 \pm 3.20$ g (Figure 2) ($P < 0.001$ versus baseline). The LV mass regression caused by eplerenone was not statistically different from that caused by enalapril ($P = 0.258$, Figure 2). Eplerenone/enalapril resulted in an adjusted mean change of $-27.2 \pm 3.39$ g in LV mass ($P < 0.001$ versus baseline), which was significantly greater than that observed in the eplerenone monotherapy group ($P = 0.007$ for eplerenone/enalapril versus eplerenone; $P = 0.107$ for eplerenone/enalapril versus enalapril; Figure 2). A further post hoc analysis was conducted to include not only the preceding patients but also those who had a baseline or final MRI more than 21 days after the first dose or last dose, respectively, of study medication, ie, outside of the prespecified windows for performing the MRIs. This analysis included an additional 5 patients. There were no significant differences in LV mass regression or comparative probability values from the results described above (data not shown).

### Results

#### Demographics and Baseline Characteristics

A total of 153 patients (eplerenone, n = 50; enalapril, n = 54; eplerenone/enalapril, n = 49) met the criteria for inclusion into the MRI cohort (ie, randomized patients who received double-blind treatment for at least 3 months and who had a baseline MRI and an end point MRI within 21 days after a dose of study medication). There were no significant differences among groups with respect to demographic or baseline characteristics, with the exception of female height (Table 1). Mean MRI LV mass and BP values were similar among groups at baseline. Demographic and baseline characteristics in the total randomized population (n = 64, 71, and 67 for eplerenone, enalapril, and eplerenone/enalapril treatment groups, respectively) were similar (data not shown) to those of MRI patients. Patient disposition is summarized in Table 2.

#### Statistical Methods

Assuming a standard deviation of 24 g in change from baseline values of LV mass, a sample size of 55 patients per group provided 94% power to detect an average reduction in LV mass within 15 g between the primary end point comparison of the eplerenone and enalapril groups (one-sided $\alpha = 0.05$).

All analyses were performed using SAS, Version 6.12 (SAS Institute). The analyses of LVH regression were conducted on the MRI cohort, which included all randomized patients who received double-blind treatment for at least 3 months and who had a baseline and an end point MRI within 21 days after a dose of double-blind study medication. Safety analyses included all randomized patients who took at least 1 dose of study medication.

Comparisons between treatment groups at baseline were evaluated using 1-way ANOVA or the $\chi^2$ test. Analysis of covariance was performed, and 95% CIs were calculated to evaluate primary and secondary treatment effects, with baseline values as covariates. For the primary efficacy variable, a 1-sided 95% lower confidence limit of treatment difference ($<-15$ g) and an equivalent 1-sided test at the 0.05 significance level were performed to establish the noninferiority of eplerenone versus enalapril.

### Data reported as mean±SD, except as noted. DBP indicates seated DBP; SBP, seated SBP. *MRI cohort included all randomized patients who received double-blind treatment for at least 3 months and who had a baseline MRI and an end point MRI within 21 days after a dose of study medication. †Statistically significant difference among treatment groups ($P = 0.044$).
Equivalency of Antihypertensive Effect

In the MRI cohort at the month 9 end point, all 3 treatment groups exhibited significant reductions from baseline in mean SBP and DBP ($\pm 23.8 \pm 1.8$ and $-11.9 \pm 1.0$ mm Hg for eplerenone; $-24.7 \pm 1.7$ and $-13.4 \pm 1.0$ mm Hg for enalapril; and $-28.7 \pm 1.8$ and $-14.4 \pm 1.0$ mm Hg for eplerenone/enalapril). These were statistically comparable, with the exception that SBP was reduced significantly more with eplerenone/enalapril than with eplerenone ($P=0.048$). Adjusted mean change from baseline in SBP and DBP in the MRI cohort for all time points is depicted in Figure 3. Overall, the rate at which SBP normalized occurred in the rank order eplerenone/enalapril >eplerenone >enalapril. However, post hoc analyses demonstrated only a poor correlation between BP control and LVH regression in any treatment arm (correlation coefficients for SBP and DBP: eplerenone, 0.201 and 0.387 ($P=0.161$ and 0.006); enalapril, 0.272 and 0.111 ($P=0.047$ and 0.422); and eplerenone/enalapril, 0.365 and 0.054 ($P=0.010$ and 0.715). To determine the effect of BP reduction on LVH regression, a post hoc analysis was performed to compare LV mass changes as a function of SBP and DBP changes. The ratio of change in LV mass to change in SBP was 0.5 for eplerenone, 0.8 for enalapril, and 0.9 for eplerenone/enalapril. Corresponding ratios for DBP were 2.3, 2.4, and 2.2. None of the comparisons achieved statistical significance. These data suggest there is no trend favoring greater changes in LV mass with greater reductions in BP.

Effects of Add-On Medications

To control for the confounding effects of BP reduction on LVH regression, the present study was designed to lower BP to equivalent levels in all 3 groups by adding HCTZ or amlodipine to patients whose DBP was not $<90$ mm Hg after eplerenone, enalapril, or eplerenone/enalapril (see Methods). This aspect of the study, although necessary for patient safety, complicated interpretation of the results, because it was possible that the additional medications influenced the observed LVH regression.

### Table 2. Patient Disposition

<table>
<thead>
<tr>
<th>Patients</th>
<th>Eplerenone 200 mg</th>
<th>Enalapril 40 mg</th>
<th>Eplerenone 200 mg/Enalapril 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients who met inclusion criteria (ie, hypertension with evidence of LVH) and were randomized</td>
<td>64</td>
<td>71</td>
<td>67</td>
</tr>
<tr>
<td>No. (%) of patients withdrawn</td>
<td>14 (21.9)</td>
<td>14 (19.7)</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td>No. (%) of patients in the MRI cohort*</td>
<td>50 (78.1)</td>
<td>54 (76.1)</td>
<td>49 (73.1)</td>
</tr>
<tr>
<td>No. (%) of patients in the MRI add-on cohort†</td>
<td>15 (30.0)</td>
<td>32 (59.3)‡</td>
<td>10 (20.4)</td>
</tr>
</tbody>
</table>

*MRI cohort included all randomized patients who received double-blind treatment for at least 3 months and who had a baseline MRI and an end point MRI within 21 days after a dose of study medication.
†MRI add-on cohort included all patients in the MRI cohort who required add-on therapy with HCTZ (12.5 or 25 mg) and/or amlodipine (10 mg) to achieve DBP $<90$ mm Hg.
‡$P<0.002$ vs eplerenone monotherapy; $P<0.001$ vs eplerenone/enalapril combination therapy.

Figure 2. Adjusted mean change in LV mass from baseline in the MRI cohort. MRI cohort included all randomized patients who received double-blind treatment for at least 3 months and who had a baseline MRI and an end point MRI within 21 days after a dose of study medication. $P<0.001$ for change from baseline within each treatment group; $*P=0.007$ for eplerenone/enalapril vs eplerenone; $\dagger P=0.107$ for eplerenone/enalapril vs enalapril; $\ddagger P=0.258$ for eplerenone vs enalapril. ENAL indicates enalapril; EPL, eplerenone.

Figure 3. Adjusted mean change from baseline over time in seated DBP and SBP in the MRI cohort. Bars represent SE of each measurement.
To determine what effect, if any, the addition of HCTZ and/or amiodipine might have had on the LVH observations, post hoc analyses were conducted for the MRI cohort. During the study, 4 patients received amiodipine therapy (4 enalapril), 34 received HCTZ therapy (11 eplerenone, 16 enalapril, and 7 eplerenone/enalapril), and 19 received amiodipine and HCTZ therapy (4 eplerenone, 12 enalapril, and 3 eplerenone/enalapril). Significantly more patients on enalapril required add-on medication to achieve DBP <90 mm Hg. Only 22 of 54 (40.7%) achieved BP control with enalapril, whereas 35 of 50 (70.0%) and 39 of 49 (79.6%) achieved control with eplerenone and eplerenone/enalapril \( (P=0.003) \) for enalapril versus eplerenone and \( P=0.001 \) for enalapril versus eplerenone/enalapril, based on \( \chi^2 \) tests. A post hoc analysis of the ratio of change in LV mass to change in SBP and DBP (Table 3) suggested that BP changes alone did not account for LVH regression.

In patients who did not require add-on therapy, LV mass decreased by 13.9 g with eplerenone, 17.9 g with enalapril, and 23.6 g with eplerenone/enalapril. The general trend for LV mass reduction seemed to be eplerenone/enalapril >enalapril >eplerenone. The differences were not statistically different, likely reflecting the relatively small number of patients in this subanalysis.

### Urinary Albumin Excretion and RAAS Hormones

Baseline geometric means for 24-hour UACR were similar among the eplerenone (13.8 mg/g), enalapril (10.8 mg/g), and eplerenone/enalapril (12.5 mg/g) groups. Treatment with eplerenone significantly decreased 24-hour UACR \( (-24.9\%) \) from baseline at the month 9 end point, as did enalapril \( (-37.4\%) \) and eplerenone/enalapril \( (-52.6\%) \). Differences between improvements in the 3 groups were significant (eplerenone/enalapril versus eplerenone, \( P=0.001 \); eplerenone/enalapril versus enalapril, \( P=0.038 \)), indicating that the renoprotective effects of eplerenone and an ACE inhibitor were additive.

Baseline levels of active plasma renin and serum aldosterone were within normal limits and similar in all 3 treatment groups. During the study, active plasma renin and serum aldosterone levels increased in the eplerenone and eplerenone/enalapril groups. In the enalapril group, active plasma renin levels increased throughout the study but serum aldosterone levels remained relatively unchanged, indicating the absence of suppression of aldosterone by as early as 12 weeks.

### Safety

All 202 patients in the randomized cohort who received at least 1 dose of study medication were included in the safety analysis. More than 78% of patients in each group continued the study for at least 8 months. Premature study discontinuation rates were similar for eplerenone (21.9%), enalapril (19.7%), and eplerenone/enalapril (16.4%). The most common reason for early discontinuation in each group was adverse events; in all, 7 patients discontinued the study because of treatment failure.

Adverse events were reported with similar incidence among treatment groups; treatment-emergent adverse events (events reported after at least 1 dose of study medication) were reported by 65.6% of eplerenone, 70.4% of enalapril, and 55.2% eplerenone/enalapril patients. Individual treatment-emergent adverse events experienced by \( \geq3\% \) of patients in any treatment group are displayed in Table 4. Cough was experienced by a significantly greater number of enalapril patients than eplerenone patients \( (P=0.033) \), and 2 patients discontinued enalapril treatment because of cough. Serious adverse events were experienced by 21 patients (7 eplerenone, 5 enalapril, and 9 eplerenone/enalapril). Only 2 of these cases were considered of probable relationship to study medication. One, a patient taking eplerenone, experienced an elevated potassium on 3 successive visits (5.7, 6.0, and 6.2 mmol/L on days 22, 36, and 40, respectively); the other, a patient taking eplerenone/enalapril, was diagnosed with cerebrovascular disorder.

Two cases of gynecomastia were reported, both of probable relationship to study medication (1 eplerenone [2.5%] and 1 eplerenone/enalapril [2.2%]). Four patients (3 enalapril

### TABLE 3. Relationship Between Change in LV Mass and Change in BP

<table>
<thead>
<tr>
<th>Group</th>
<th>SBP Change, mm Hg</th>
<th>Ratio of Change in LV Mass to Change in SBP</th>
<th>DBP Change, mm Hg</th>
<th>Ratio of Change in LV Mass to Change in DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No add-on therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>-27.4</td>
<td>0.5</td>
<td>-14.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>-23.8</td>
<td>1.3</td>
<td>-14.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Eplerenone/enalapril</td>
<td>-28.8</td>
<td>0.8</td>
<td>-14.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Therapy with HCTZ (n=34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>-16.6</td>
<td>0.3</td>
<td>-5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Enalapril</td>
<td>-22.8</td>
<td>0.2</td>
<td>-10.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Eplerenone/enalapril</td>
<td>-18.8</td>
<td>2.0</td>
<td>-12.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Therapy with HCTZ and AML (n=19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>-18.6</td>
<td>0.4</td>
<td>-8.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>-30.1</td>
<td>0.7</td>
<td>-17.3</td>
<td>-0.5</td>
</tr>
<tr>
<td>Eplerenone/enalapril</td>
<td>-52.3</td>
<td>0.9</td>
<td>-25.0</td>
<td>2.2</td>
</tr>
</tbody>
</table>

AML indicates amiodipine.
patients, thereby eliminating the potentially confounding factors that may influence the interpretation of this study is the number of subjects who required add-on medication to achieve BP control. This number was significantly higher in the enalapril arm than in the other 2 arms. An analysis of those patients who did not require add-on medication suggests that both eplerenone and enalapril were equally effective in reducing LV mass at an equivalent reduction in BP. However, given the greater reduction in SBP in the combination arm, we cannot with certainty separate the effects of the combination on BP reduction and reduction in LV mass. Regardless, combination treatment provides an additive benefit on both BP reduction and LV mass reduction.

As with LV mass reduction, eplerenone and enalapril were similarly effective in reducing albuminuria, with the combination being significantly more effective than either agent alone. Although the level of albuminuria was modest, recent data suggest that any degree of albuminuria is associated with an increase in subsequent cardiovascular events.11

In the present study, there was a relatively poor correlation between the effect of eplerenone (alone or in combination with enalapril) on the change in BP and its effect on reducing LV mass. A similar poor correlation has been reported in previous studies, including LIFE,12 suggesting that other factors may be as important or more important for reducing effects of differential BP reduction on LVH regression. This was attempted by allowing the addition of HCTZ and/or amlodipine to achieve a DBP <90 mm Hg. Equivalency of diastolic, but not systolic, BP in the 3 treatment arms was achieved. For the primary end point, reduction in LV mass, eplerenone, and enalapril caused highly significant, equivalent reductions from baseline. The decrease in LV mass with combination therapy was significantly greater than that seen with eplerenone alone and greater than enalapril alone, although the latter difference did not reach statistical significance (Figure 2).

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**Discussion**

Target-organ protection in patients with essential hypertension has become increasingly important. Because agents that lower BP equally do not necessarily have equivalent effects on reducing target-organ damage and consequent morbidity and mortality, an important component of the present study was the effort to achieve equivalent BP reduction in all patients, thereby eliminating the potentially confounding effects of differential BP reduction on LVH regression. This was attempted by allowing the addition of HCTZ and/or amlodipine to achieve a DBP <90 mm Hg. Equivalency of diastolic, but not systolic, BP in the 3 treatment arms was achieved. For the primary end point, reduction in LV mass, eplerenone, and enalapril caused highly significant, equivalent reductions from baseline. The decrease in LV mass with combination therapy was significantly greater than that seen with eplerenone alone and greater than enalapril alone, although the latter difference did not reach statistical significance (Figure 2).

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**TABLE 4. Adverse Events Experienced by >3% in Any Treatment Group**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eplerenone 200 mg</th>
<th>Enalapril 40 mg</th>
<th>Eplerenone 200 mg/Enalapril 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=64)</td>
<td>(n=71)</td>
<td>(n=67)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (9.4)</td>
<td>4 (5.6)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (9.4)</td>
<td>10 (14.1)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (7.8)</td>
<td>2 (2.8)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4 (6.3)</td>
<td>1 (1.4)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>4 (6.3)</td>
<td>4 (5.6)</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (6.3)</td>
<td>5 (7.0)</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>4 (6.3)</td>
<td>2 (2.8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (4.7)</td>
<td>4 (5.6)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (4.7)</td>
<td>6 (8.5)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2 (3.1)</td>
<td>5 (7.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Coughing</td>
<td>2 (3.1)</td>
<td>10 (14.1)</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>0 (0.0)</td>
<td>4 (5.6)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Impotence</td>
<td>0 (0.0)</td>
<td>3 (4.5)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Potassium &gt;6 mEq/L</td>
<td>7 (10.9)</td>
<td>2 (2.8)</td>
<td>3 (4.5)</td>
</tr>
</tbody>
</table>

Data reported as n (%).

*P=0.033 vs eplerenone monotherapy.
†According to laboratory results, not adverse event reports.
‡P=0.084 vs eplerenone monotherapy.

[6.6%] and 1 eplerenone/enalapril [2.2%]) experienced impotence during the study. The latter adverse events were mild or moderate in severity, and 3 were considered by the investigator to be of uncertain relationship to study medication. None of these events was serious or led to premature withdrawal. There were no reports of menstrual disorders or female breast pain in any study arm.

Seven eplerenone (10.9%), 2 enalapril (2.8%), and 3 eplerenone/enalapril patients (4.5%) had serious hyperkalemia (a maximum potassium level >6.0 mmol/L on 1 occasion; upper limit of normal for the central laboratory was 5.4 mmol/L). However, no clinical symptoms or complications of hyperkalemia were observed in any of these patients. Three patients in the eplerenone group were withdrawn because of hyperkalemia (K+ = 5.7, 5.8, and 6.2 mmol/L on the last day of study medication). All other cases of elevated potassium resolved spontaneously without discontinuation or dose modification of study medication. No patients in the enalapril or eplerenone/enalapril groups were withdrawn for hyperkalemia.

Serum creatinine levels >2.0 mg/dL were reported for 2 patients during the study (1 with eplerenone and 1 with eplerenone/enalapril). There were no significant differences among groups with respect to mean change in vital signs, and there were no abnormal ECG results attributed to study medication.
LV mass than BP reduction per se. However, one must exercise caution in concluding that reduction in BP is not of critical importance in reducing target-organ damage. This study was designed to normalize BP in all treatment arms and achieved equality in diastolic but not systolic pressure. One could argue that because BP was reduced similarly, the equivalent reduction in LV mass in the enalapril and eplerenone arms was secondary to the reduction in BP. However, in the present study, LV mass reduction in the combination arm was nearly twice as great as with either treatment alone, although the reduction in SBP was only slightly, albeit significantly, greater compared with monotherapy with eplerenone.

The mechanisms responsible for the beneficial cardiovascular effect of mineralocorticoid receptor blockade on LVH are not clear. Similar uncertainty exists for the mechanisms by which reducing Ang II levels have a beneficial effect. Of particular interest is the known association of both agents in activating NADH/NADPH-dependent oxidase activity, which has been shown to be important in Ang II–induced LVH. Both hormones also increase intracellular calcium concentration, which could lead to hypertrophy of the myocyte. Finally, aldosterone can increase the number of AT1 receptors and tissue ACE activity, which could result in a vicious cycle whereby interfering with either aldosterone or Ang II could have beneficial effects.

Aldosterone levels were not elevated at baseline in the present study. Normal serum levels of aldosterone in conjunction with the elevated sodium intake of a Western diet may inappropriately activate the mineralocorticoid receptor and/or increase tissue levels of aldosterone. Mineralocorticoid receptors can be occupied by cortisol as well as by aldosterone. Occupancy of the mineralocorticoid receptor by cortisol may increase because of a reduction in the activity of the enzyme 11β-HSD2. This enzyme converts cortisol to corticosterone, which cannot activate the mineralocorticoid receptor. Increases in the activity of the enzyme 11β-HSD1, which increases the availability of cortisol, may be upregulated. Thus, under circumstances of increased oxidative stress (eg, hypertension), the occupancy and transcriptional activity of the mineralocorticoid receptor by cortisol may be increased. Because eplerenone is an equally effective competitive antagonist for either hormone at the mineralocorticoid receptor, its beneficial effects may be secondary to blockade of the action of either or both.

Eplerenone, alone or in combination with an ACE inhibitor, seems to be a promising therapy for reducing LVH, and therefore reducing morbidity and mortality, in patients with essential hypertension. The optimal dose-response relationship of eplerenone and/or an ACE inhibitor remains to be determined. As anticipated, both eplerenone and enalapril modestly increased serum potassium levels. This effect may in part account for the greater cardiovascular protective effects of agents that interrupt the RAAS. Importantly, elevated potassium levels in this study were not associated with any adverse clinical outcomes. The only significant difference in adverse events among the 3 groups was an increase in the frequency of cough in the enalapril group.

Mancia et al reported that patients with essential hypertension whose BP is adequately controlled (eg, <140/90 mm Hg) with antihypertensive medication have a 20% incidence of LVH compared with normotensive individuals. These results reinforce the need for better control of BP and of target-organ damage. Data from LIFE suggest that blockade of the Ang II receptor by losartan results in a reduction in LVH, cardiovascular morbidity, and mortality, independent of its effects on BP. Blockade of the mineralocorticoid receptor may have a similar beneficial effect on regression of LVH and albuminuria and therefore possibly on morbidity and mortality in patients with essential hypertension, whereas blockade or inhibition of both aldosterone and Ang II has additive effects. However, this hypothesis must be substantiated in prospective randomized studies powered to evaluate morbidity and mortality.

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Effects of Eplerenone, Enalapril, and Eplerenone/Enalapril in Patients With Essential Hypertension and Left Ventricular Hypertrophy: The 4E–Left Ventricular Hypertrophy Study

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