Eplerenone Reduces Mortality 30 Days After Randomization Following Acute Myocardial Infarction in Patients With Left Ventricular Systolic Dysfunction and Heart Failure

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OBJECTIVES This study sought to assess the impact of the selective aldosterone blocker eplerenone on mortality 30 days after randomization in patients after acute myocardial infarction (AMI) with a left ventricular ejection fraction (LVEF) ≤40% and clinical signs of heart failure.

BACKGROUND In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced all-cause mortality by 15% (p = 0.008) over a mean follow-up of 16 months when used with standard therapy in patients after AMI with an LVEF ≤40% and clinical signs of heart failure.

METHODS We analyzed the effect of eplerenone 25 mg/day initiated 3 to 14 days after AMI (mean, 7.3 days) on the co-primary endpoints of time to death from any cause and the composite end point of time to death from cardiovascular (CV) causes or hospitalization for CV events, and the secondary end point of CV mortality, sudden cardiac death, and fatal/nonfatal hospitalization for heart failure, after 30 days of therapy in the EPHESUS trial.

RESULTS At 30 days after randomization, eplerenone reduced the risk of all-cause mortality by 31% (3.2% vs. 4.6% in eplerenone and placebo-treated patients, respectively; p = 0.004) and reduced the risk of CV mortality/CV hospitalization by 13% (8.6% vs. 9.9% in eplerenone and placebo-treated patients, respectively; p = 0.074). Eplerenone also reduced the risk of CV mortality by 32% (p = 0.003) and the risk of sudden cardiac death by 37% (p = 0.051).

CONCLUSIONS Eplerenone 25 mg/day significantly reduced all-cause mortality 30 days after randomization (when initiated at a mean of 7.3 days after AMI) in addition to conventional therapy in patients with an LVEF ≤40% and signs of heart failure. Based on its early survival benefit, eplerenone should be administered in the hospital after AMI. (J Am Coll Cardiol 2005;46: 425–31) © 2005 by the American College of Cardiology Foundation

Reduced left ventricular ejection fraction (LVEF) (≤40%) and/or signs of clinical heart failure early after acute myocardial infarction (AMI) are associated with a relatively high incidence of mortality and hospitalization for heart failure (1–5). Of importance, patients with signs of heart failure post-infarction have a three- to four-fold increased risk of in-hospital death and a 55% increased risk of dying within 30 days after AMI in comparison with patients with an acute infarction but no signs of heart failure (1–6). This early increase in risk in patients with a reduced LVEF and clinical signs of heart failure argues for therapeutic intervention as early as possible after AMI.

To gain insight into the potential of eplerenone to impact early mortality post-infarction, we examined the results 30 days after randomization from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (7). In this trial, the selective aldosterone blocker eplerenone was shown to significantly reduce all-cause mortality by 15% (p = 0.008) and the composite end point of cardiovascular (CV) mortality/CV hospitalization by 13% (p = 0.002) over a mean follow-up of 16 months when added to standard therapy in post-AMI patients with an LVEF ≤40% and clinical signs of heart failure.

METHODS

Study design and population. The study design and overall findings of the EPHESUS trial have been described previously (7). Briefly, this multicenter, double-blind, randomized, international trial included 6,632 patients with AMI complicated by left ventricular systolic dysfunction.
Eplerenone Reduces Early Mortality After AMI

Results

As noted in the EPHESUS trial (7), baseline characteristics between placebo- and eplerenone-treated patients were similar (Table 1). The mean age in the EPHESUS trial was 64 years; the mean LVEF was 33%. The majority of the population was Caucasian (90%) and male (71%). In both groups, the mean time from AMI to randomization was 7.3 days. Approximately 65% of patients in both groups were classified as Killip class II at randomization, and 90% of patients in both groups had signs of clinical heart failure (10% had diabetes mellitus without clinical heart failure). At baseline, the majority of patients were receiving conventional standard therapies for AMI complicated by LVSD and heart failure, and in general these medications were continued throughout the 30-day study period: 87% of the EPHESUS trial patients were receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs); 75%, beta-blockers; 60%, diuretics; 88%, aspirin; and 47%, statins. In both treatment groups, 45% of patients received coronary reperfusion therapy. The index AMI in approximately 73% of patients in both treatment groups was the patient’s first AMI, a majority of these (71%) being Q-wave AMIs. Only 14% of eplerenone-treated and 15% of placebo-treated patients had a history of heart failure.

End points. Event rates 30 days after randomization for eplerenone-treated and placebo-treated patients are given in Table 2. Compared with placebo, eplerenone significantly reduced the risk for the primary end point of all-cause mortality. After 30 days of treatment, 107 patients (3.2%) treated with eplerenone and 153 patients (4.6%) receiving placebo died, resulting in a risk reduction of 31% with eplerenone (95% confidence interval [CI] 0.54 to 0.89; p = 0.004) (Fig. 1A). The co-primary end point of CV mortality/CV hospitalization occurred in 287 eplerenone-treated (8.6%) and 329 placebo-treated patients (9.9%) by 30 days after randomization, for a risk reduction of 13% (95% CI 0.74 to 1.01; p = 0.074) with eplerenone (Fig. 1B). For the secondary end point of CV mortality, eplerenone reduced the relative risk by 32% (95% CI 0.53 to 0.88; p = 0.003) compared with placebo at 30 days (Fig. 1C). The most common cause of CV mortality after AMI was sudden cardiac death, which occurred in 30 eplerenone-treated (0.9%) and 47 placebo-treated patients (1.4%) at 30 days after randomization, resulting in a risk reduction of 37% with eplerenone compared with placebo (p = 0.051) (Fig. 1D). The relative risk of fatal or nonfatal hospitalization for heart failure 30 days after randomization was reduced non-significantly by 18% with eplerenone (p = 0.106).

The relative risk for all-cause mortality 30 days after randomization in important predefined subgroups (by base-
line demographics, clinical characteristics, and therapy) is given in Figure 2. Risk reductions with eplerenone were consistent among the subgroups.

**Safety.** A full description of the safety results from the EPHESUS trial has been previously published (7). After 30 days of treatment, a similar number of patients in both treatment groups discontinued therapy (139 in the placebo group, 134 in the eplerenone group). During this time, 49% of placebo-treated patients and 48% of eplerenone-treated patients experienced at least one adverse event ($p = 0.29$). Most adverse events occurred in fewer than 1% of patients; these events included hypokalemia, which occurred in 4 placebo-treated patients (0.12%) and 7 eplerenone-treated patients (0.21%) ($p = 0.548$ placebo vs. eplerenone), and hyperkalemia, which occurred in 15 placebo-treated patients (0.45%) and 23 eplerenone-treated patients (0.69%)

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eplerenone Group (n = 3,319)</th>
<th>Placebo Group (n = 3,313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ± SD)</td>
<td>64 ± 12</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,380 (72)</td>
<td>2,234 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>939 (28)</td>
<td>979 (30)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2,995 (90)</td>
<td>2,989 (90)</td>
</tr>
<tr>
<td>Black</td>
<td>30 (1)</td>
<td>44 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>294 (9)</td>
<td>280 (8)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg ± SD)</td>
<td>119/72 ± 17/11</td>
<td>119/72 ± 17/11</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 ± 6</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl ± SD)</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Serum potassium (mmol/l ± SD)</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>Time from AMI to randomization (days ± SD)</td>
<td>7.3 ± 3.0</td>
<td>7.3 ± 3.0</td>
</tr>
</tbody>
</table>

**Index AMI**
- Q-wave (%) | Eplerenone Group: 69.5, Placebo Group: 72.3
- Non-Q-wave (%) | Eplerenone Group: 28.6, Placebo Group: 25.9

**Reperfusion therapy (%)**
- PTCR: Eplerenone Group: 23.6, Placebo Group: 24.1
- CABG: Eplerenone Group: 0.9, Placebo Group: 1.2

**Medical history (%)**
- AMI: Eplerenone Group: 27, Placebo Group: 27
- Diabetes mellitus: Eplerenone Group: 32, Placebo Group: 32
- Heart failure: Eplerenone Group: 14, Placebo Group: 15
- Hypertension: Eplerenone Group: 60, Placebo Group: 61

**Documentation of heart failure (%)**
- Pulmonary rales: Eplerenone Group: 74.2, Placebo Group: 75.7
- Pulmonary venous congestion on chest radiograph: Eplerenone Group: 34.6, Placebo Group: 34.0
- Third heart sound: Eplerenone Group: 24.8, Placebo Group: 25.3
- None (diabetic patients only): Eplerenone Group: 10.1, Placebo Group: 9.8

**Baseline medications (%)**
- Beta-blocker: Eplerenone Group: 75, Placebo Group: 75
- Diuretics: Eplerenone Group: 60, Placebo Group: 61
- Aspirin: Eplerenone Group: 88, Placebo Group: 89
- Statins: Eplerenone Group: 47, Placebo Group: 47

*Data are for medications taken at randomization or up to 14 days after the index acute myocardial infarction (AMI). Plus-minus values are mean ± SD.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; PTCR = percutaneous transluminal coronary revascularization.

### Table 2. Summary of End Points at 30 Days After Randomization

<table>
<thead>
<tr>
<th>End Point</th>
<th>Eplerenone Group (n = 3,319)</th>
<th>Placebo Group (n = 3,313)</th>
<th>Risk Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, n (%)</td>
<td>107 (3.2%)</td>
<td>153 (4.6%)</td>
<td>0.69 (0.54, 0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Death from CV causes or hospitalization* for CV events, n (%)</td>
<td>287 (8.6%)</td>
<td>329 (9.9%)</td>
<td>0.87 (0.74, 1.01)</td>
<td>0.074</td>
</tr>
<tr>
<td>Death from CV causes, n (%)</td>
<td>101 (3.0%)</td>
<td>147 (4.4%)</td>
<td>0.68 (0.53, 0.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sudden cardiac death, n (%)</td>
<td>30 (0.9%)</td>
<td>47 (1.4%)</td>
<td>0.63 (0.40, 1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Fatal/nonfatal HF hospitalization, n (%)</td>
<td>114 (3.4%)</td>
<td>138 (4.2%)</td>
<td>0.82 (0.64, 1.04)</td>
<td>0.106</td>
</tr>
</tbody>
</table>

*Hospitalizations are nonfatal events causing or prolonging hospitalizations, cardiovascular (CV) events could include heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia.

CI = confidence interval; HF = heart failure.
After 30 days of treatment, mean serum potassium increased by 0.17 mmol/l in placebo-treated patients and by 0.24 mmol/l in eplerenone-treated patients (p < 0.001); mean serum potassium at four weeks after randomization was 4.47 mmol/l and 4.54 mmol/l in placebo-treated and eplerenone-treated patients, respectively. As shown in Figure 2, the benefit of eplerenone on all-cause mortality was consistent regardless of whether patients were above or below the baseline median value for serum potassium of 4.0 mmol/l.

At 30 days after randomization, placebo-treated patients experienced significantly greater increases in sitting systolic and diastolic blood pressure (4.0 ± 0.4 mm Hg and 2.9 ± 0.2 mm Hg, respectively) than patients treated with eplerenone (2.4 ± 0.4 mm Hg and 1.7 ± 0.2 mm Hg, respectively; p = 0.001 for systolic blood pressure changes, placebo vs. eplerenone; p = 0.008 for diastolic blood pressure changes, placebo vs. eplerenone). Changes in resting heart rate at 30 days after randomization were similar between the treatment groups, −4.0 ± 0.3 beats/min with placebo, and −4.3 ± 0.3 beats/min with eplerenone; p > 0.20.

DISCUSSION

This analysis shows that eplerenone, at a dose of 25 mg/day, reduced total mortality by 31% (p = 0.004) and CV mortality by 32% (p = 0.003) within 30 days of randomization after AMI. This is important because 25% of total deaths occurring over the mean 16-month follow-up in placebo-treated patients in the EPHESUS trial occurred within the first 30 days after randomization. Of particular interest was the finding that eplerenone reduced sudden cardiac death by 37% (p = 0.051) within 30 days of randomization. There was a modest but non-significant 13% (p = 0.074) reduction in the co-primary end point of CV mortality/CV hospitalization and an 18% reduction (p = 0.106) in fatal/nonfatal heart failure hospitalization within 30 days after randomization. Risk reduction in all-cause mortality with eplerenone seemed to occur as early as 10 days after randomization (Fig. 1) and continued through the end of the study (the mean duration of follow-up was 16 months). Importantly, the reduction in mortality 30 days after randomization with eplerenone occurred in patients receiving an ACE inhibitor or ARB and a beta-blocker as well as in patients receiving “optimal therapy” including an ACE inhibitor or ARB, beta-blocker, aspirin, statin, and having undergone coronary reperfusion. Although study medication could be titrated upward to 50 mg after 30 days based on serum potassium levels in the EPHESUS trial, this analysis shows that the lower dose of eplerenone, 25 mg/day, showed significant reductions in mortality and morbidity within 30 days.

Aspirin, coronary reperfusion, ACE inhibitors, beta-blockers, and statins seem to be most effective when administered within the early hours after AMI (8,9). There is also evidence showing that an aldosterone-blocking agent can be administered safely to patients within the first 24 h
post-infarction and that this practice imparts an early beneficial effect on ventricular remodeling. Hayashi et al. (10) found that an aldosterone-blocking strategy was effective in preventing left ventricular remodeling and myocardial collagen formation when administered to patients with a first anterior AMI immediately after primary angioplasty, within 24 h post-infarction. Of importance, both in the study by Hayashi et al. (10) and in the present study, it was observed that the addition of an aldosterone blocker to patients on an ACE inhibitor or an ARB and a beta-blocker was well tolerated and did not cause significant hypotension.

A theoretical concern regarding administration of eplerenone early post-infarction is that the prevention of myocardial collagen formation could adversely affect healing of the infarct scar and therefore predispose to cardiac rupture and/or aneurysm formation. Experimental studies have shown, however, that eplerenone does not interfere with infarct scar healing but does prevent reactive fibrosis in areas remote from the infarct zone (11), which may influence left ventricular remodeling and prognosis. Neither experimental nor clinical administration of aldosterone blockade early post-infarction has been associated with any detrimental effect (10,11). Given all of the above, it is possible that these beneficial results on 30-day mortality underestimate the potential of eplerenone to reduce early mortality after AMI because the mean time from onset of infarction to randomization in the EPHESUS trial was 7.3 days, the time interval with the highest mortality after AMI. The explanation for the early reduction in total mortality by eplerenone in the EPHESUS trial is probably multifactorial because the adverse cardiovascular effects of aldosterone or activation of the mineralocorticoid receptor are manifold. Electrical remodeling of the myocardium after experimental AMI is evident within one week and precedes myocyte hypertrophy (12). After experimental myocardial infarction, there is an increase in myocardial calcium current

![Figure 2. Relative risk of death from any cause according to baseline demographic and clinical characteristics. The data represented are hazard ratios with 95% confidence intervals. Values for age, pulse pressure, serum potassium concentration, serum creatinine concentration, left ventricular ejection fraction (LVEF), and body mass index were dichotomized at the median value. Analyses according to the use of an angiotensin-converting enzyme inhibitor (ACEI) (or angiotensin receptor blocker [ARB]), a beta-blocker (BB), or both; according to the use of an ACEI (or ARB) with a BB, aspirin (ASA), statins, and reperfusion therapy up to 14 days after the index acute myocardial infarction (AMI); according to the use of diuretics; and according to the use of lipid-lowering agents were post-hoc analyses. PTCA = percutaneous transluminal coronary angioplasty.](image-url)
of the myocardium can be prevented by mineralocorticoid receptor blockade (12).

The early benefits of eplerenone on all-cause mortality may also be attributable to its ability to prevent ventricular remodeling and myocardial collagen formation. Plasma aldosterone is extracted through the heart after an AMI, and this correlates positively with one month left ventricular end-diastolic volume index and plasma levels of procollagen type III aminoterminal peptide (PIIINP), a biochemical marker of cardiac collagen synthesis (13). The importance of the effect of aldosterone blockade on collagen formation is emphasized by the finding in the EPHESUS trial that collagen formation, as assessed by PIIINP, correlated with all-cause mortality and was significantly reduced with eplerenone (14).

In another study in patients with a first anterior myocardial infarction, an aldosterone-blocking strategy administered one day post-infarction after percutaneous transluminal coronary angioplasty significantly attenuated ventricular remodeling and collagen formation in comparison with placebo by 30 days post-infarction (10). The reduction in left ventricular remodeling with aldosterone blockade is important because ventricular remodeling is associated with the activation of neurohormones including angiotensin II, aldosterone, endothelin, and norepinephrine, along with various cytokines and growth factors, production of reactive oxygen species, apoptosis, and collagen formation, all of which can predispose to sudden cardiac death (15–17).

Aldosterone blocks myocardial neuronal norepinephrine uptake, thereby preventing its intracardiac metabolism and disposal; conversely, aldosterone blockade has been shown to improve myocardial neuronal uptake of norepinephrine and to decrease plasma norepinephrine levels, QT interval, and ventricular arrhythmias (18,19). Aldosterone blockade has also been shown to improve heart rate variability and baroreceptor function and to reduce central sympathetic nervous system activity (20–22). These effects, all of which may contribute to decreased mortality, occur relatively early post-infarction. It is therefore likely that the sum of the effects of aldosterone blockade, rather than any individual mechanism, accounts for the beneficial effects of eplerenone on total mortality within 30 days after randomization in the EPHESUS trial.

Several recent studies have underscored the high risk in the period early after AMI (1–3,6). Although the peak incidence of total mortality, cardiac death, and sudden cardiac death occurs relatively early post-infarction, these events may occur at any time after AMI. This is especially true in patients with persistent LVSD, in whom the long-term risk of death caused by progressive heart failure may be as great as or greater than that of sudden cardiac death. Thus, in patients with LVSD and signs of heart failure, it would seem prudent to initiate eplerenone in hospital following hemodynamic stabilization after AMI and to continue eplerenone in addition to an ACE inhibitor or an ARB and a beta-blocker over the long term.

**REFERENCES**