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Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

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ABSTRACT

BACKGROUND

Aldosterone blockade reduces mortality and morbidity among patients with severe heart failure. We conducted a double-blind, placebo-controlled study evaluating the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

METHODS

Patients were randomly assigned to eplerenone (25 mg per day initially, titrated to a maximum of 50 mg per day; 3313 patients) or placebo (3319 patients) in addition to optimal medical therapy. The study continued until 1012 deaths occurred. The primary end points were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia.

RESULTS

During a mean follow-up of 16 months, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (relative risk, 0.85; 95 percent confidence interval, 0.75 to 0.96; P=0.008). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to cardiovascular causes (relative risk, 0.83; 95 percent confidence interval, 0.72 to 0.94; P=0.005). The rate of the other primary end point, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (relative risk, 0.87; 95 percent confidence interval, 0.79 to 0.95; P=0.002), as was the secondary end point of death from any cause or any hospitalization (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.98; P=0.02). There was also a reduction in the rate of sudden death from cardiac causes (relative risk, 0.79; 95 percent confidence interval, 0.64 to 0.97; P=0.03). The rate of serious hyperkalemia was 5.5 percent in the eplerenone group and 3.9 percent in the placebo group (P=0.002), whereas the rate of hypokalemia was 8.4 percent in the eplerenone group and 13.1 percent in the placebo group (P<0.001).

CONCLUSIONS

The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

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Aldosterone blockade reduces the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes, as well as the rate of hospitalizations for heart failure, among patients with severe heart failure due to systolic left ventricular dysfunction who are being treated with an angiotensin-converting–enzyme (ACE) inhibitor.[1] Aldosterone blockade also prevents ventricular remodeling and collagen formation in patients with left ventricular dysfunction after acute myocardial infarction[2] and affects a number of pathophysiological mechanisms that are thought to be important in the prognosis of patients with acute myocardial infarction.[3-12] Its role in reducing mortality and the rate of hospitalization among patients with acute myocardial infarction complicated by left ventricular dysfunction is uncertain. We therefore designed the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) to test the hypothesis that treatment with eplerenone, an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not glucocorticoid, progesterone, or androgen receptors,[13] reduces overall mortality and cardiovascular mortality or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure who are receiving optimal medical therapy.

METHODS

STUDY DESIGN AND STUDY POPULATION

We conducted a multicenter, international, randomized, double-blind, placebo-controlled trial.[14] Patients were randomly assigned to receive eplerenone (25 mg per day) or matching placebo for four weeks, after which the dose of eplerenone was increased to a maximum of 50 mg per day. Randomization was stratified according to clinical site, and schedules were prepared with the use of permuted blocks to ensure the ongoing equivalence of the size of the groups. If at any time during the study the serum potassium concentration was higher than 5.5 mmol per liter, the dose of the study drug was reduced or treatment was temporarily discontinued until the serum potassium concentration fell below 5.5 mmol per liter.

Patients in whom the following criteria were met were eligible for randomization 3 to 14 days after acute myocardial infarction: acute myocardial infarction as documented according to standard criteria; left ventricular dysfunction as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute myocardial infarction, symptoms of heart failure did not have to be demonstrated, since such patients have an increased risk of cardiovascular events similar to that of nondiabetic patients with symptoms of heart failure.[15] Patients received optimal medical therapy, which could include ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy.

Important criteria for exclusion were the use of potassium-sparing diuretics, a serum creatinine concentration of more than 2.5 mg per deciliter (220 μmol per liter), and a serum potassium concentration of more than 5.0 mmol per liter before randomization. The institutional review board or ethics committee at each site approved the protocol, and all patients provided written informed consent before enrollment.

Screening and base-line procedures were to be performed during the hospitalization for the index acute myocardial infarction, and follow-up visits occurred at one and four weeks, three months, and every three months thereafter until the termination of the study. The serum potassium concentration was measured 48 hours after the initiation of treatment, at one, four, and five weeks, at all scheduled study visits, and within one week after any change of dose. Information about adverse events and concurrent medications was recorded at every visit. All patients who underwent randomization were followed for vital status and hospitalizations every three months until the termination of the study.

DEFINITION OF STUDY END POINTS

The two primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia. The major secondary end points were death from cardiovascular causes and death from any cause or any hospitalization. All end points were adjudicat-

ed by a blinded critical-events committee. Definitions of all adjudicated end points are presented in Supplementary Appendix 1 (available with the full text of this article at http://www. nejm.org).

STATISTICAL ANALYSIS

The two groups were compared in terms of the two primary end points and the secondary end points with the use of Cox proportional-hazards regression. The Cox model included a single covariate corresponding to treatment group and was stratified according to geographic region (Canada and the United States, Latin America, eastern Europe, western Europe, and the rest of the world [including Australia, Israel, New Zealand, South Africa, South Korea, and Taiwan]). The model was used to estimate the relative risk and corresponding 95 percent confidence interval. Time-to-event distributions were summarized with Kaplan–Meier curves. For analyses of mortality, data were censored at the time of loss to follow-up or on the closing date of the study (August 30, 2002). For analyses of death from cardiovascular causes or hospitalization for cardiovascular events, data were censored at the time of death due to noncardiovascular causes, the time of loss to follow-up, or on the closing date of the study. Analyses of the primary and secondary end points were conducted according to the intention-to-treat principle.

The trial was designed to enroll 6200 patients and to continue until 1012 deaths occurred. To maintain an overall type I error rate of 0.05 (two-sided), the rate of death from any cause was tested at the 0.04 level of significance and the rate of death from cardiovascular causes or hospitalization for cardiovascular events was tested at the 0.01 level of significance. With testing at the 0.04 level of significance (two-sided), the study had 88.3 percent power to detect an 18.5 percent difference between the two groups in the rate of death from any cause.[16] An external data and safety monitoring board conducted four interim analyses; an alpha level of 0.0001 was the threshold for early termination in the first two interim analyses of mortality from any cause, and an alpha level of 0.001 was the threshold for the last two analyses. Data-base management was performed by a contract research organization. The interim analyses were conducted by an independent statistician for the data and safety monitoring board. All final analyses were conducted by the sponsor. All independent authors had a substantial role in trial design, data accrual, and data interpretation. All had complete access to the data after unblinding.

Subgroup analyses for the two primary end points were performed with a Cox model stratified according to region, with terms for treatment, subgroup, and interaction between treatment and subgroup. For these analyses, measured variables were treated as binary variables, dichotomized at the median value, and also considered as continuous variables.

We also used Cox regression to summarize the time to first hospitalization for a cardiovascular event. For these analyses, data were censored at the time of death. The frequencies of hospitalization for particular causes were analyzed by means of a Cochran–Mantel–Haenszel test, and the relative risk for this analysis was reported as the ratio of the number of hospitalizations per patient in the eplerenone group to the number of hospitalizations per patient in the placebo group. The number of patients who would need to be treated to prevent one event was determined by the method of Altman and Andersen.[17]

All patients who received at least one dose of the study medication were included in the safety analyses, which included analyses of adverse events, vital signs, and results of clinical laboratory tests. Changes in vital signs and clinical laboratory values were assessed by analysis of covariance, with the base-line value as a covariate. Creatinine clearance was calculated according to the Cockcroft–Gault formula.[18] All reported P values are two-sided and are not adjusted for the interim analyses.

RESULTS

STUDY PATIENTS

A total of 6642 patients underwent randomization at 674 centers in 37 countries between December 27, 1999, and December 31, 2001. A total of 3313 were assigned to placebo, 3319 were assigned to eplerenone, and 10 were excluded from the analysis before unblinding because of problems with the quality of the data at one center. There were no significant differences between the two groups at base line (Table 1). At base line, the majority of patients were receiving standard therapies for acute myocardial infarction complicated by left ventricular dysfunction and heart failure, including ACE inhibitors or angiotensin-receptor blockers (in 87 percent of patients), beta-blockers (in 75 percent), aspirin (in 88 percent), and diuretics (in 60 percent).

Twelve patients in each treatment group did not take any study medication. During the study, 1021 patients (493 in the placebo group and 528 in the eplerenone group) permanently discontinued the

study medication (median time from randomization to the last dose, 98 days). The most frequent reasons were a request by the patient to withdraw from the study (in 204 patients in the placebo group and 231 in the eplerenone group) and adverse events (in 149 patients in the placebo group and 147 in the eplerenone group). Seventeen patients (7 in the placebo group and 10 in the eplerenone group) had unknown vital status on the closing date of the study (August 30, 2002), and 99 percent of the surviving patients were seen or contacted between August 15 and August 30, 2002. The mean duration of follow-up was 16 months (range, 0 to 33). The mean dose-equivalent of study medication was 43.5 mg in the placebo group and 42.6 mg in the eplerenone group.

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Eplerenone Group (N=3319)	Placebo Group (N=3313)
Age — yr	64±11	64±12
Race — no. (%)†		
White	2995 (90)	2989 (90)
Black	30 (1)	44 (1)
Other	294 (9)	280 (8)
Sex — no. (%)		
Male	2380 (72)	2334 (70)
Female	939 (28)	979 (30)
Blood pressure — mm Hg		
Systolic	119±17	119±17
Diastolic	72±11	72±11
Left ventricular ejection fraction — %	33±6	33±6
Days from myocardial infarction to randomization	7.3±3.0	7.3±3.0
Previous hospitalization for heart failure — %	7	8
Reperfusion therapy or revascularization — %	45	45
Symptoms of heart failure — %	90	90
Serum potassium concentration — mmol/liter	4.3±0.4	4.3±0.5
Serum creatinine concentration — mg/dl‡	1.1±0.3	1.1±0.3
Creatinine clearance — ml/min	79±60	78±57
Medical history — %		
Acute myocardial infarction	27	27
Diabetes	32	32
Heart failure	14	15
Hypertension	60	61
Medications — %§		
ACE inhibitor or angiotensin-receptor blocker	86	87
Beta-blockers	75	75
Diuretics	60	61
Aspirin	88	89
Statins	47	47

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme.
† Race was self-reported by patients.
‡ To convert values for creatinine to micromoles per liter, multiply by 88.4.
§ Data are for medications taken at randomization or up to 14 days after the index acute myocardial infarction.

END POINTS

A total of 478 patients in the eplerenone group (14.4 percent) and 554 patients in the placebo group (16.7 percent) died (relative risk, 0.85; P=0.008) (Table 2). Kaplan–Meier estimates of mortality at one year were 11.8 percent in the eplerenone group and 13.6 percent in the placebo group (Fig. 1A). The end point of death from cardiovascular causes or hospitalization for cardiovascular events was reached by 885 patients in the eplerenone group (26.7 percent) and 993 patients in the placebo group (30.0 percent) (relative risk, 0.87; P=0.002) (Fig. 1B).

A total of 407 deaths in the eplerenone group (12.3 percent of patients) and 483 deaths in the placebo group (14.6 percent of patients) were attributed to cardiovascular causes (relative risk, 0.83; P=0.005). The reduction in cardiovascular mortality was similar for the most common causes — sudden death from cardiac causes, acute myocardial infarction, and heart failure (range of relative risks, 0.79 to 0.82). Of these reductions, the reduction in the risk of sudden death from cardiac causes was statistically significant (relative risk, 0.79; P=0.03) (Table 2 and Fig. 1C). There was a relative reduction of 15 percent in the risk of hospitalization for heart failure with eplerenone (relative risk, 0.85; P=0.03), and there were 23 percent fewer episodes of hospitalization for heart failure in the eplerenone group than in the placebo group (relative risk, 0.77; P=0.002). The rate of death from any cause or any hospitalization was 8 percent lower in the eplerenone group than in the placebo group (relative risk, 0.92; P=0.02).

The relative risks for important predefined subgroups are shown in Figure 2. Reductions in the rate of death from any cause and the rate of death from cardiovascular causes or hospitalization for cardiovascular events were consistent among subgroups. Interactions between treatment and some measured variables were significant when they

Table 2. Summary of Primary and Secondary End Points.*

Variable	Eplerenone Group (N=3319)	Placebo Group (N=3313)	Relative Risk (95% CI) or Ratio†	P Value
Primary end points				
Death from any cause (no. of patients)	478	554	0.85 (0.75–0.96)	0.008
Death from cardiovascular causes or hospitalization for cardiovascular events (no. of patients)	885	993	0.87 (0.79–0.95)	0.002
Secondary end points				
Death from any cause or any hospitalization (no. of patients)	1730	1829	0.92 (0.86–0.98)	0.02
Death from cardiovascular causes (no. of patients)	407	483	0.83 (0.72–0.94)	0.005
Sudden death from cardiac causes	162	201	0.79 (0.64–0.97)	0.03
Acute myocardial infarction	78	94	0.82 (0.61–1.10)	0.19
Heart failure	104	127	0.80 (0.62–1.04)	0.10
Stroke	26	28	0.91 (0.53–1.55)	0.73
Other	37	33	1.00 (0.60–1.66)	0.99
Any hospitalization (no. of patients)	1493	1526	0.95 (0.89–1.02)	0.20
Hospitalization for cardiovascular events (no. of patients)	606	649	0.91 (0.81–1.01)	0.09
Acute myocardial infarction	224	229	0.97 (0.80–1.16)	0.71
Heart failure	345	391	0.85 (0.74–0.99)	0.03
Stroke	70	51	1.34 (0.94–1.93)	0.11
Ventricular arrhythmia	52	54	0.95 (0.65–1.39)	0.79
Any hospitalization (no. of episodes)	2815	2984	0.94	0.12
Hospitalization for cardiovascular events (no. of episodes)	876	1004	0.87	0.03
Acute myocardial infarction	268	269	0.99	0.96
Heart failure	477	618	0.77	0.002
Stroke	73	54	1.35	0.11
Ventricular arrhythmia	58	63	0.92	0.69

* Hospitalizations were defined as nonfatal events causing or prolonging hospitalization. CI denotes confidence interval.
† Numbers without confidence intervals are the ratios of the number of hospitalizations per patient in the eplerenone group to the number of hospitalizations per patient in the placebo group.

were analyzed as binary variables with median cutoff points (e.g., pulse pressure), but when they were considered as continuous variables, the interactions were no longer significant. The beneficial effect of eplerenone was also consistent across geographic regions (P=0.24 for the interaction of treatment and region for death from any cause, and P=0.94 for the interaction of treatment and region for death from cardiovascular causes or hospitalization for cardiovascular events).

SAFETY

After week 1, the mean systolic and diastolic blood pressure increased in both groups from base line to each time point throughout the remainder of the trial. The magnitude of these increases in the

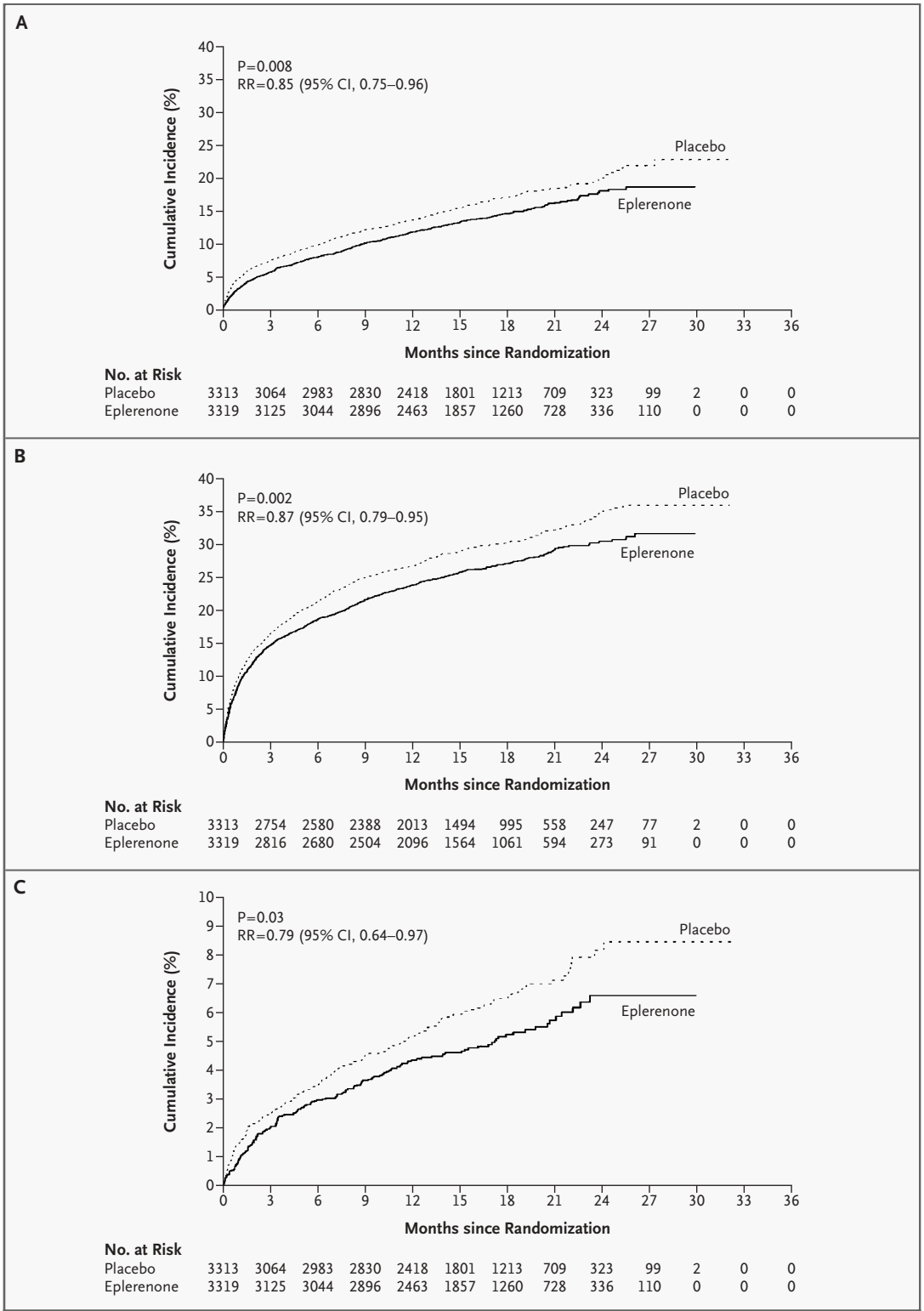


Figure 1. Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C).
RR denotes relative risk, and CI confidence interval.

eplerenone group was significantly smaller than that in the placebo group at every point. At one year, the mean blood pressure had increased by 8/4 mm Hg in the placebo group and by 5/3 mm Hg in the eplerenone group (P<0.01). Also at one year, the heart rate had decreased by 6 beats per minute in the placebo group and by 7 beats per minute in the eplerenone group (P=0.32).

At one year, the serum creatinine concentration had increased by 0.02 mg per deciliter (1.8 μmol per liter) in the placebo group and by 0.06 mg per deciliter (5.3 μmol per liter) in the eplerenone group (P<0.001). Potassium levels had increased in both groups at one year (by 0.2 mmol per liter in the placebo group and 0.3 mmol per liter in the eplerenone group, P<0.001). Serious hyperkalemia (serum potassium concentration, ≥6.0 mmol per liter) occurred in 5.5 percent of patients in the eplerenone group, as compared with 3.9 percent of those in the placebo group (P=0.002). For patients who had serious hyperkalemia, the incidence of greater elevations in the potassium concentration was similar in the eplerenone group (0.6 percent with concentrations ≥7 mmol per liter and 0.2 percent with concentrations ≥8 mmol per liter) and in the placebo group (0.5 percent with concentrations ≥7 mmol per liter and 0.1 percent with concentrations ≥8 mmol per liter). Fifteen patients with serious hyperkalemia (12 in the eplerenone group and 3 in the placebo group) were hospitalized for the condition, and one death in the placebo group was attributed to it. In each treatment group, the incidence of hyperkalemia was higher among patients with a lower base-line creatinine clearance (P<0.001 by logistic-regression analysis). Among patients with a base-line creatinine clearance of less than 50 ml per minute, the incidence of serious hyperkalemia was 10.1 percent in the eplerenone group and 5.9 percent in the placebo group (P=0.006). Among patients with a base-line creatinine clearance of 50 ml per minute or more, the corresponding rates were 4.6 percent and 3.5 percent (P=0.04). Patients who had serious hyperkalemia were also more likely than those who did not have serious hyperkalemia to have a serum potassium concentration of more than 5.5 mmol per liter or a calculated creatinine clearance of less than 70 ml per minute at the week 1 visit.

There were no other significant differences between the treatment groups in the number of patients with changes in laboratory variables that met prespecified criteria for abnormally low or high values. Adverse events are described in Table 3.

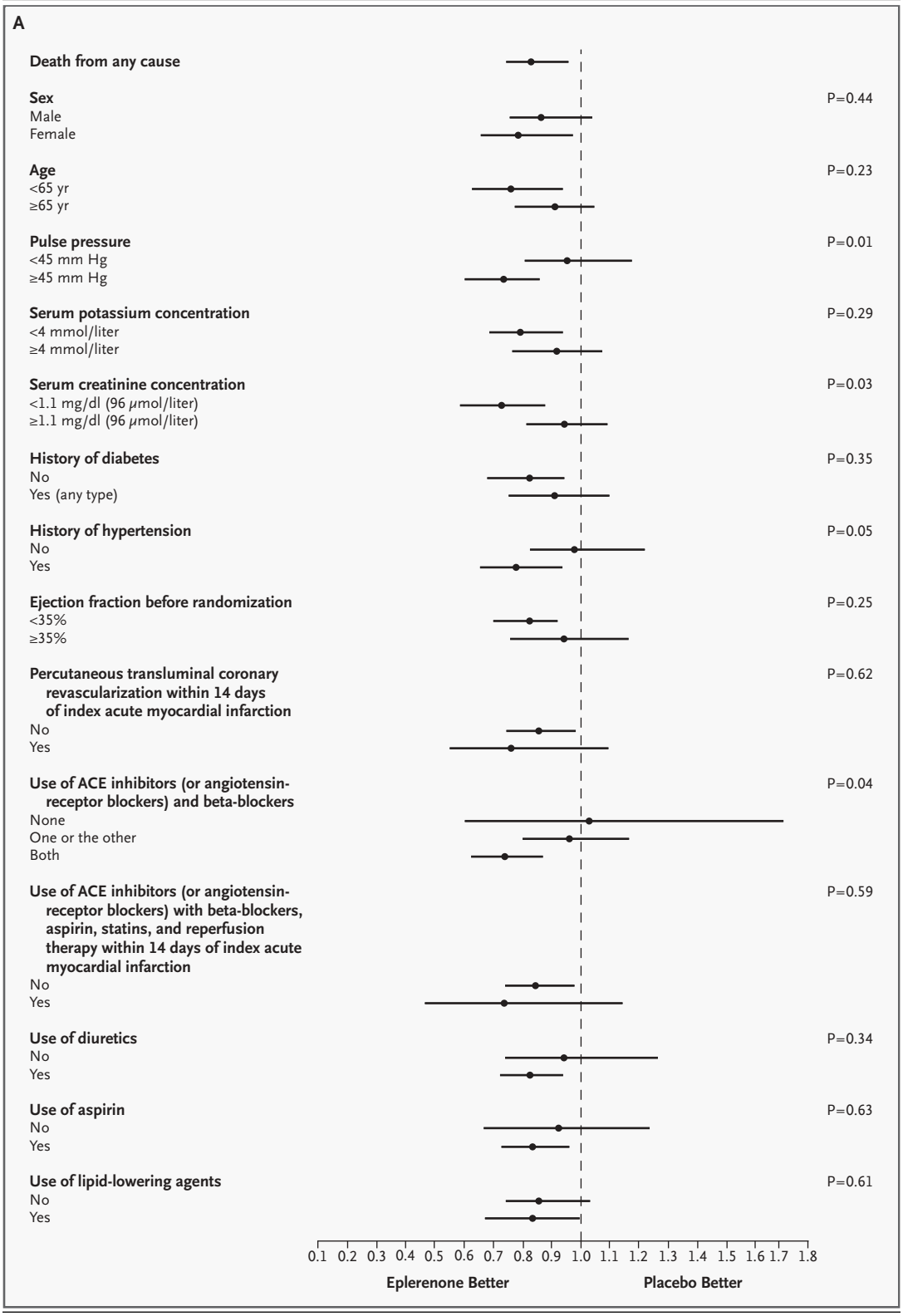
DISCUSSION

The addition of eplerenone to optimal treatment at a maximal dose of 50 mg once daily (mean dose, 43 mg per day) in patients assigned to treatment 3 to 14 days (mean, 7) after acute myocardial infarction resulted in additional reductions in overall mortality and the rate of death from cardiovascular causes or hospitalization for cardiovascular events among patients whose acute myocardial infarction was complicated by left ventricular dysfunction and heart failure. There was also a reduction in cardiovascular mortality and the rate of death from any cause or any hospitalization among patients assigned to eplerenone.

One-year mortality among patients assigned to placebo, the majority of whom received an ACE inhibitor or angiotensin-receptor blocker and a beta-blocker, was 13.6 percent. This rate is higher than that in the treatment groups of a recent study of carvedilol in patients with left ventricular dysfunction after acute myocardial infarction (the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction [CAPRICORN] study) and a study of losartan in patients with left ventricular dysfunction after acute myocardial infarction (the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan [OPTIMAAL]),[19,20] in which control patients were treated with an ACE inhibitor and a beta-blocker; the higher rate in our study most likely reflects the presence of signs of heart failure, in addition to left ventricular dysfunction, in 90 percent of our patients. Mortality in the placebo group in the current study, however, was lower and the

Figure 2. Relative Risks of Death from Any Cause (Panel A, next page) and Relative Risks of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B, page 1317), According to Base-Line Demographic and Clinical Characteristics.

Horizontal lines represent 95 percent confidence intervals. Values for age, pulse pressure, serum potassium concentration, serum creatinine concentration, and ejection fraction were dichotomized at the median. Analyses according to the use or nonuse of an angiotensin-converting–enzyme (ACE) inhibitor (or angiotensin-receptor blocker), a beta-blocker, or both; according to the use of an ACE inhibitor (or angiotensin-receptor blocker) with a beta-blocker, aspirin, statins, and reperfusion therapy up to 14 days after the index acute myocardial infarction; according to the use of diuretics; and according to the use of lipid-lowering agents were post hoc analyses.



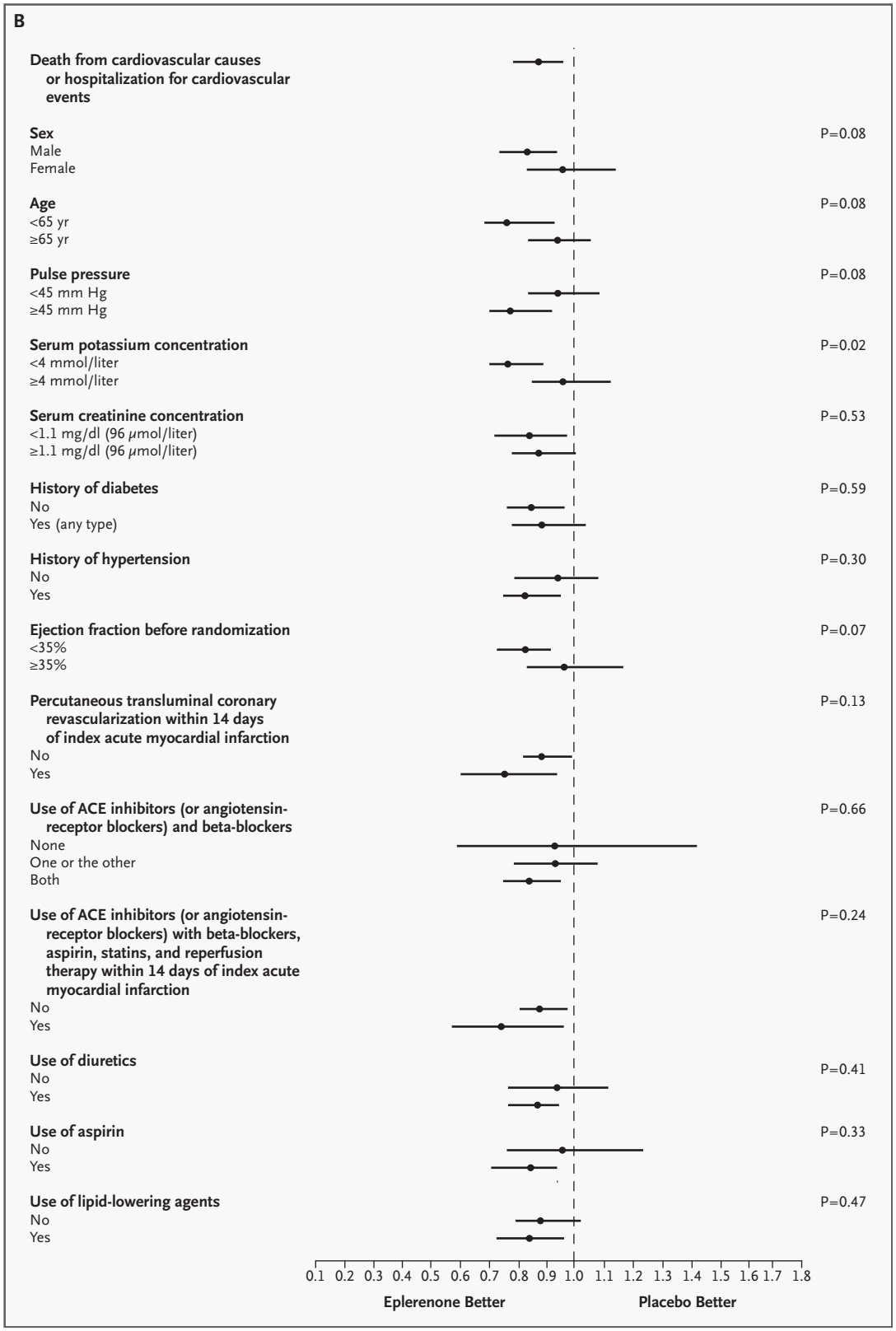


Table 3. Adverse Events.

Adverse Event	Eplerenone Group (N=3307)	Placebo Group (N=3301)	P Value
	no. of patients (%)		
≥1 Event	2608 (78.9)	2623 (79.5)	0.57
Cardiovascular disorder*	1606 (48.6)	1661 (50.3)	0.16
Respiratory disorder	729 (22.0)	803 (24.3)	0.03
Cough	167 (5.0)	207 (6.3)	0.03
Dyspnea	243 (7.3)	307 (9.3)	0.004
Pneumonia	92 (2.8)	123 (3.7)	0.03
Metabolic or nutritional disorder	568 (17.2)	635 (19.2)	0.03
Hyperkalemia†	113 (3.4)	66 (2.0)	<0.001
Hypoglycemia	20 (0.6)	35 (1.1)	0.04
Hypokalemia†	15 (0.5)	49 (1.5)	<0.001
Hyperuricemia	87 (2.6)	111 (3.4)	0.08
Neoplasm	57 (1.7)	58 (1.8)	0.93
Urinary tract disorder	473 (14.3)	419 (12.7)	0.06
Disorder of skin or appendages	220 (6.7)	223 (6.8)	0.88
Musculoskeletal disorder	209 (6.3)	213 (6.5)	0.84
Nervous system disorder	492 (14.9)	449 (13.6)	0.14
Psychiatric disorder	238 (7.2)	272 (8.2)	0.12
Gastrointestinal disorder	659 (19.9)	583 (17.7)	0.02
Endocrine disorder	34 (1.0)	23 (0.7)	0.18
Disorder in men‡	59 (2.5)	65 (2.8)	0.53
Gynecomastia	12 (0.5)	14 (0.6)	0.70
Impotence	21 (0.9)	20 (0.9)	1.00
Disorder in women§	17 (1.8)	17 (1.7)	1.00
Breast pain	1 (0.1)	3 (0.3)	0.63
Serious hyperkalemia (serum potassium ≥6 mmol/liter)¶	180 (5.5)	126 (3.9)	0.002
Serious hypokalemia (serum potassium <3.5 mmol/liter)¶	273 (8.4)	424 (13.1)	<0.001

* Data are for all cardiovascular adverse events reported, whether or not they were related to a study end point.
† Data are based on investigators' reports.
‡ There were 2326 men in the placebo group and 2370 men in the eplerenone group.
§ There were 975 women in the placebo group and 937 women in the eplerenone group.
¶ Data are based on laboratory measurements. Data were available for 3237 patients in the placebo group and 3251 in the eplerenone group.

magnitude of the effect of aldosterone blockade was smaller than in the Randomized Aldactone Evaluation Study (RALES), a trial of spironolactone in patients with left ventricular dysfunction and severe chronic heart failure.[1] These differences may be attributable to several factors, including the greater use of beta-blockers and a higher base-line left ventricular ejection fraction in the current study. In RALES,[1] the mean left ventricular ejection fraction at base line was 25 percent, and patients had New York Heart Association class III or IV heart failure, whereas in the current study in patients with acute myocardial infarction, the mean left ventricular ejection fraction was 33 percent at base line and may have improved after reperfusion, recovery of ventricular stunning, or both. The severity of left ventricular dysfunction,[21] the degree of heart failure, and the intensity of background therapy are most likely important factors determining the absolute mortality as well as the effectiveness of therapeutic agents.

The reduction in cardiovascular mortality was in large part due to a 21 percent reduction in the rate of sudden death from cardiac causes. Reductions in the rate of death due to progressive heart failure and acute myocardial infarction were similar but not significant. The reduction in the rate of hospitalization for cardiovascular events was largely due to a 15 percent reduction in the risk of hospitalization for heart failure and a 23 percent reduction in the number of episodes of hospitalization for heart failure. The mechanisms by which eplerenone provides myocardial protection in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure are not completely clear. Effects of aldosterone blockers on plasma volume and electrolyte excretion have been recognized for many years, and although these effects may have contributed to the benefit provided by eplerenone, other nonrenal mechanisms may be equally or more important. Eplerenone reduces coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis in animal models of myocardial disease.[22,23] Eplerenone also reduces oxidative stress, improves endothelial dysfunction,[4,24] attenuates platelet aggregation,[4] decreases activation of matrix metalloproteinases, and improves ventricular remodeling.[25] In addition, aldosterone blockade decreases sympathetic drive in rats through direct actions in the brain,[26] improves norepinephrine uptake in patients with heart failure,[3] and improves heart-rate variability[27]

— all factors known to have important effects on the risk of sudden death from cardiac causes.

Eplerenone was beneficial in patients who were receiving optimal therapy including an ACE inhibitor or angiotensin-receptor blocker, a beta-blocker, aspirin, a lipid-lowering agent, and coronary reperfusion therapy. Previous experience with regard to the effectiveness of aldosterone blockade in patients with left ventricular dysfunction who are receiving an ACE inhibitor and a beta-blocker is limited, in that in RALES the proportion of patients who were treated with a beta-blocker was only 11 percent.[1] This difference in treatments is important, because ACE inhibitors and beta-blockers are considered to represent the current standard of care in patients with left ventricular dysfunction after acute myocardial infarction, and other treatments, including endothelin-receptor antagonists, antibodies against tumor necrosis factor α, and angiotensin-receptor blockers, have not been found to reduce mortality among patients with left ventricular dysfunction and heart failure who are being treated with an ACE inhibitor and a beta-blocker.

We examined a number of predefined subgroups, but our trial was not designed with sufficient power to draw statistical conclusions about individual subgroups. Thus, one should be cautious in interpreting the results of subgroup analyses. There were a few subgroups in which we found a nominally significant interaction with treatment, but no interaction we examined had a significant effect on both primary end points. In general, the beneficial effect of eplerenone on the two primary end points was consistent.

There was an increased incidence of serious hyperkalemia among patients assigned to eplerenone. The risk of serious hyperkalemia was significantly increased among patients who had a decreased creatinine clearance at base line (<50 ml per minute). Although there were no deaths in the eplerenone group that were attributed to hyperkalemia, this finding emphasizes the need to monitor serum potassium and adjust the dose of eplerenone accordingly. We attempted to minimize the risk of hyperkalemia by excluding patients with a base-line serum potassium concentration of more than 5.0 mmol per liter, a base-line serum creatinine concentration of more than 2.5 mg per deciliter, or both. It should, however, be emphasized that in elderly patients, patients with a low body-mass index, or patients with diabetes mellitus, the serum creatinine concentration may not accurately reflect renal function. Determination of creatinine clearance by the Cockcroft–Gault formula, exclusion of patients with moderate-to-severe renal insufficiency, use of a loop diuretic in those with mild renal insufficiency, and adherence to the range of doses used in this study (25 to 50 mg per day) should minimize the risk of hyperkalemia among patients receiving eplerenone and further improve the risk–benefit ratio of this drug. It should also be pointed out that the risk of hypokalemia was more than twice as high as the risk of serious hyperkalemia and that eplerenone significantly reduced this risk.

The rate of discontinuation of blinded treatment due to adverse events and the rates of adverse events other than hyperkalemia and a variety of minor gastrointestinal complications in patients receiving eplerenone were low. In particular, the incidence of gynecomastia and impotence among men in the eplerenone group was no greater than that in the placebo group. This finding differs from the findings in RALES[1] and can be attributed to the fact that eplerenone has greater selectivity for the mineralocorticoid receptor than does spironolactone, which also binds to androgen and progesterone receptors. The benefit of eplerenone in reducing the risk of respiratory disorders most likely reflects its reduction of the rate of recurrent heart failure, whereas its benefit in reducing the risk of metabolic and nutritional disorders largely reflects a reduced incidence of hypokalemia and hypoglycemia.

In conclusion, with an estimated number needed to treat of 50 to save one life in one year and an estimated number needed to treat of 33 to prevent one death from cardiovascular causes or one hospitalization for a cardiovascular event in one year, the addition of eplerenone to optimal medical therapy contributes to the continued improvement in survival and hospitalization rates among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

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Drs. Pitt and Zannad report having served as consultants to Pharmacia.

APPENDIX

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