EDITORIAL

Aldosterone Antagonists — Last Man Standing?

Paul W. Armstrong, M.D.

The transformation of cardiac care over the past half century has been breathtaking to witness. In large part, this transformation is due to the advent of new drugs and devices, improved health care systems, and behavioral modifications such as smoking cessation. Four cardiac medicines developed before 1960 that survived the turn of the millennium are aspirin, digoxin, warfarin, and spironolactone. New competitors threaten the continued longevity of aspirin, the survival of digoxin depends on evidence of its ability to improve exercise tolerance and quality of life in patients with heart failure, and new pretenders for warfarin are here. Remarkably, after over 50 years, the aldosterone antagonism achieved by spironolactone (and more recently eplerenone) has earned an enduring role in the treatment of heart failure.[1]

When spironolactone was developed, it was a minor player complementing more powerful diuretics in achieving volume homeostasis. Our understanding of heart failure was then predominantly focused on hemodynamic perturbations. As long ago as 1960, the drug was found to protect rats against myocardial necrosis,[2] yet this observation languished for decades. Subsequently, two parallel tracks of knowledge emerged, which are germane to a resurgence of interest in antagonizing aldosterone. The first track involves the complex adaptations affecting the failing and remodeled heart. Cardiac enlargement and increased sphericity are often accompanied by scarring and fibrosis. Neurohormonal activation and altered vascular compliance of coronary and peripheral blood vessels compound this unfavorable milieu.[3] The second track concerns the pleiotropic effects of aldosterone antagonists. These include conservation of potassium and magnesium, the depletion of which potentiates ventricular arrhythmias and sudden death; inhibition of fibroblast proliferation and perivascular fibrosis, which are promoted by chronic hyperaldosteronism; and reversal of unfavorable coronary and renal vascular remodeling, which is modulated by endothelial-cell and baroreceptor dysfunction.[3]

These physiological observations now appear to have important clinical consequences. In the Randomized Aldactone Evaluation Study (RALES), Pitt and colleagues[4] demonstrated that spironolactone therapy could significantly reduce rates of death and hospital readmission for worsening heart failure among patients with functional class III or IV heart failure. Four years after this seminal study, the same investigators conducted the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[5] which showed that eplerenone, a selective aldosterone-receptor blocker, reduced morbidity and mortality among patients recovering from acute myocardial infarction with complicating left ventricular dysfunction. As a result of these convincing findings, aldosterone-receptor blockade has become part of recommended therapy in such patients.[6]

In this issue of the *Journal,* Zannad and colleagues[7] complete an aldosterone-trial trilogy with their report on the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF; ClinicalTrials.gov number, NCT00232180), which shows that eplerenone reduces the rate of death from cardiovascular causes or hospitalization for heart failure by approximately 37%, as compared with placebo, in patients with functional class II heart failure. Although this effect seems surprisingly large for a trial of mildly symptomatic patients, careful review of the baseline characteristics is instructive.

The majority of the study patients were heart disease veterans: one half had previously been

hospitalized for heart failure and had a history of myocardial infarction; hypertension, atrial fibrillation, and diabetes were also common. The mean ejection fraction of 26% (nearly identical to that in the more severely symptomatic patients in RALES) is a cogent reminder of the discordance between functional class and left ventricular function. An additional feature marking the EMPHASIS-HF patients as high risk is that approximately one quarter had left bundle-branch block, and the overall mean QRS duration was 122 msec (with one quarter having a QRS duration >130 msec). Although the concomitant use of beta-blockers and angiotensin-converting–enzyme inhibitors was common, the infrequent use of implantable defibrillators or cardiac resynchronization therapy raises the question of whether eplerenone would have fared as impressively had a larger proportion of the study population received implantable electrical devices, in alignment with current guidelines.[6] This points to the need for further investigation, given that even the trial participants receiving active therapy had a 1-year mortality rate of approximately 5.0%.

The effect on death from cardiovascular causes or hospitalization for heart failure translates into an impressively low number needed to treat: 19 patients. The number needed to treat to prevent one death is 51 patients, positioning this therapy in the front rank of therapeutic choices. The survival curves invite speculation about whether the effect of eplerenone on volume homeostasis came into play early, thereby affecting hospitalization for heart failure sooner, whereas structural changes such as favorable cardiac remodeling might have accounted for the more delayed reduction in mortality.

The EMPHASIS-HF investigators have added real value to the management of heart failure. Since spironolactone is available for pennies a day, one might reasonably ask whether the greater cost of eplerenone is warranted or whether it is reasonable to simply assume that the current findings also apply to spironolactone and reserve the newer, more expensive therapy for those few patients in whom the side effects of spironolactone are disabling. I believe this would be a reasonable tactic. It is now time to overcome undertreatment by ensuring that this form of therapy is incorpo-

rated into all heart-failure regimens.[8] It is incumbent on the prescriber to perform appropriate monitoring of renal and electrolyte status, which can enhance the safety of such treatment.[9]

As one reflects on the EMPHASIS-HF results, the question arises: Do they open doors for investigating aldosterone antagonism in other cardiovascular diseases? The answer is, most emphatically, yes. In fact, studies of this therapy in patients with diastolic dysfunction and acute myocardial infarction are ongoing, and the results are eagerly awaited. A preventive approach in patients at high cardiovascular risk might even be on the horizon.[10] Of the quartet of therapies that have served us well over the past half century, aldosterone antagonism seems most likely to be the last man standing.

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ORIGINAL ARTICLE

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

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ABSTRACT

BACKGROUND

Mineralocorticoid antagonists improve survival among patients with chronic, severe systolic heart failure and heart failure after myocardial infarction. We evaluated the effects of eplerenone in patients with chronic systolic heart failure and mild symptoms.

METHODS

In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

RESULTS

The trial was stopped prematurely, according to prespecified rules, after a median follow-up period of 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio, 0.63; 95% confidence interval [CI], 0.54 to 0.74; P<0.001). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (hazard ratio, 0.76; 95% CI, 0.62 to 0.93; P=0.008); 10.8% and 13.5%, respectively, died of cardiovascular causes (hazard ratio, 0.76; 95% CI, 0.61 to 0.94; P=0.01). Hospitalizations for heart failure and for any cause were also reduced with eplerenone. A serum potassium level exceeding 5.5 mmol per liter occurred in 11.8% of patients in the eplerenone group and 7.2% of those in the placebo group (P<0.001).

CONCLUSIONS

Eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms. (Funded by Pfizer; ClinicalTrials.gov number, NCT00232180.)

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THE ACTIVATION OF MINERALOCORTI-coid receptors by aldosterone and cortisol has deleterious effects in patients with cardiovascular disease.[1] In the placebo-controlled Randomized Aldactone Evaluation Study (RALES),[2] adding the mineralocorticoid-receptor antagonist spironolactone to recommended therapy in patients with systolic heart failure and moderate-to-severe symptoms (i.e., New York Heart Association [NYHA] functional class III or IV symptoms) decreased the rate of death from any cause and the risk of hospitalization for cardiovascular reasons. In the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[3] the selective mineralocorticoid-receptor antagonist eplerenone, added to recommended medical therapy, reduced the rates of death from any cause and hospitalization for cardiovascular reasons among patients with acute myocardial infarction complicated by left ventricular systolic dysfunction and heart failure. Consequently, current guidelines recommend the use of a mineralocorticoid-receptor antagonist in these patients.[4,5]

The aim of our Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) was to investigate the effects of eplerenone, added to evidence-based therapy, on clinical outcomes in patients with systolic heart failure and mild symptoms (i.e., NYHA functional class II symptoms).[6]

METHODS

STUDY OVERSIGHT

The executive steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed and oversaw the conduct of the trial and data analysis in collaboration with representatives of the study sponsor (Pfizer). The trial was monitored by an independent data and safety monitoring committee. Data were collected, managed, and analyzed by the sponsor according to a predefined statistical analysis plan, and the analyses were replicated by an independent academic statistician. The manuscript was prepared by an academic writing group, whose members had unrestricted access to the data, and was subsequently revised by all the authors. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data and analyses.

STUDY PATIENTS

The design of the EMPHASIS-HF trial has been published in detail,[6] and the trial protocol and statistical analysis plan are available at NEJM.org. The trial was approved by each center's ethics committee. All patients provided written informed consent.

Eligibility criteria were as follows: an age of at least 55 years, NYHA functional class II symptoms, an ejection fraction of no more than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography), and treatment with an angiotensin-converting–enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose.

Randomization was to occur within 6 months after hospitalization for a cardiovascular reason. Patients who had not been hospitalized for a cardiovascular reason within 6 months before the screening visit could be enrolled if the plasma level of B-type natriuretic peptide (BNP) was at least 250 pg per milliliter or if the plasma level of N-terminal pro-BNP was at least 500 pg per milliliter in men and 750 pg per milliliter in women.

Key exclusion criteria were acute myocardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol per liter, an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m² of body-surface area, a need for a potassium-sparing diuretic, and any other clinically significant, coexisting condition.

STUDY PROCEDURES

We used a computerized randomization system involving concealed study-group assignments to randomly assign patients to receive eplerenone (Inspra, Pfizer) or matching placebo. Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m²), provided the serum potassium level was no more than 5.0 mmol per liter.

Thereafter, investigators evaluated patients every 4 months and were instructed to decrease the dose of the study drug if the serum potassium level was 5.5 to 5.9 mmol per liter and to withhold the study drug if the serum potassium level was 6.0 mmol per liter or more. Potassium

was to be remeasured within 72 hours after the dose reduction or study-drug withdrawal, and the study drug was to be restarted only if the level was below 5.0 mmol per liter.

STUDY OUTCOMES

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The prespecified adjudicated secondary outcomes were hospitalization for heart failure or death from any cause, death from any cause, death from cardiovascular causes, hospitalization for any reason, and hospitalization for heart failure, among others (listed in Table 2). Adjudication of the outcomes was carried out by an independent committee (see the Supplementary Appendix) according to prespecified criteria.

STATISTICAL ANALYSIS

The initial assumptions were that, with 2584 patients and an annual event rate of 18% in the placebo group (based on data from a subgroup analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added trial [CHARM-Added; ClinicalTrials .gov number, NCT00634309]),[7] our trial would require 813 patients with a primary outcome occurring within 48 months to achieve 80% power to detect an 18% relative reduction in the risk of the primary outcome in the eplerenone group as compared with the placebo group (with a two-sided alpha of 0.05). Because the overall blinded event rate was lower than expected, the sample size was increased to 3100 patients, according to a protocol amendment adopted in June 2009.

The data and safety monitoring committee's charter specified interim analyses of the primary outcome after approximately 271 and 542 events had occurred, with a statistical stopping guideline for an overwhelming benefit (two-sided P<0.001 in favor of eplerenone). On May 6, 2010, after the second interim analysis, the data and safety monitoring committee reported to the executive committee chairs that the prespecified stopping boundary for an overwhelming benefit had been crossed. The full executive committee was informed, decided to stop the trial, and notified the sponsor of this decision on May 9, 2010. Operationally, May 25, 2010, was chosen as the trial cutoff date for all efficacy and safety analyses reported here.

Comparability of baseline characteristics between the two study groups was assessed by means of a two-sample t-test, for continuous variables, or Fisher's exact test, for categorical variables. The analyses of the adjudicated primary and secondary outcomes were conducted on data from all patients who had undergone randomization, according to the intention-to-treat principle, with the use of Kaplan–Meier estimates and Cox proportional-hazards models. Hazard ratios, 95% confidence intervals, and P values were calculated with the use of models adjusted for the following prespecified baseline prognostic factors: age, estimated GFR, ejection fraction, body-mass index, hemoglobin value, heart rate, systolic blood pressure, diabetes mellitus, history of hypertension, previous myocardial infarction, atrial fibrillation, and left bundle-branch block or QRS duration greater than 130 msec. Sensitivity analyses were also performed, by means of unadjusted Cox models.

The consistency of the treatment effect was assessed among 20 prespecified subgroups. The effect in each subgroup was analyzed with the use of a Cox proportional-hazards model, without adjustment for covariates. The treatment-by-subgroup interaction was evaluated by means of a Cox proportional-hazards model with terms for treatment, subgroup, and their interaction.

The number of patients who would need to be treated to prevent one primary-outcome event from occurring was determined according to the method of Altman and Andersen.[8] Post hoc comparisons between the two groups of the total number of hospitalizations for any reason and for heart failure were performed with the use of a t-test, assuming a Poisson distribution. Serious adverse events, anticipated adverse events, and adverse events leading to permanent study-drug withdrawal were tabulated according to randomized group assignment and analyzed by means of Fisher's exact test.

RESULTS

STUDY PATIENTS

From March 30, 2006, through May 25, 2010, we recruited 2737 patients at 278 centers in 29 countries. Of these patients, 1364 were randomly assigned to eplerenone and 1373 to placebo. The two groups were balanced with respect to baseline characteristics, and all the patients were receiving recommended pharmacologic therapy for systolic heart failure (Table 1).

A total of 45 patients (3.3%) in the eplerenone group and 51 patients (3.7%) in the placebo group were enrolled on the basis of a QRS duration that was greater than 130 msec (with an ejection fraction >30 to 35%); 195 patients (14.3%) in the eplerenone group and 190 patients (13.8%) in the placebo group were enrolled on the basis of the BNP or N-terminal pro-BNP criterion (with no hospitalization for cardiovascular reasons within the 180 days before screening). Half the patients reported having had a myocardial in-farction, but all cases of infarction had occurred more than 30 days before the screening visit.

STUDY-DRUG ADMINISTRATION AND FOLLOW-UP

Eight patients (four in each study group) did not start the study medication and were not included in the safety analysis. After completion of the dose-adjustment phase, at 5 months, 60.2% of patients who had been assigned to receive eplere-none were taking the higher dose (50 mg daily); the corresponding proportion in the placebo

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Eplerenone (N=1364)	Placebo (N=1373)
Age — yr	68.7±7.7	68.6±7.6
Female sex — no. (%)	309 (22.7)	301 (21.9)
Race — no. (%)†		
White	1127 (82.6)	1141 (83.1)
Black	37 (2.7)	30 (2.2)
Asian	158 (11.6)	158 (11.5)
Other	42 (3.1)	44 (3.2)
Heart rate — beats/min	72±12	72±13
Blood pressure — mm Hg		
Systolic	124±17	124±17
Diastolic	75±10	75±10
Left ventricular ejection fraction — %	26.2±4.6	26.1±4.7
QRS duration — msec	121±45	122±44
QRS duration >130 msec in nonpaced baseline ECG — no./total no. (%)	298/1167 (25.5)	305/1158 (26.3)
Body-mass index‡	27.5±4.9	27.5±4.9
Principal cause of heart failure — no. (%)		
Ischemic heart disease	951 (69.7)	935 (68.1)
Nonischemic heart disease	410 (30.1)	436 (31.8)
Unknown	3 (0.2)	2 (0.1)
Duration of heart failure — yr	4.8±5.9	4.6±5.5
Medical history — no. (%)		
Hospitalization for heart failure	714 (52.3)	726 (52.9)
Hypertension	910 (66.7)	909 (66.2)
Angina pectoris	590 (43.3)	599 (43.6)
Myocardial infarction	686 (50.3)	695 (50.6)
PCI	300 (22.0)	296 (21.6)
CABG	256 (18.8)	260 (18.9)
Atrial fibrillation or flutter	409 (30.0)	435 (31.7)
Left bundle-branch block in nonpaced baseline ECG	304/1171 (26.0)	316/1158 (27.3)
Diabetes mellitus	459 (33.7)	400 (29.1)
Stroke	136 (10.0)	126 (9.2)

Table 1. (Continued.)		
Characteristic	Eplerenone (N = 1364)	Placebo (N = 1373)
Hemoglobin — g/dl	13.8±1.6	13.8±1.6
Serum creatinine — mg/dl	1.14±0.30	1.16±0.31
Estimated GFR — ml/min/1.73 m² of body-surface area	71.2±21.9	70.4±21.7
Estimated GFR rate <60 ml/min/1.73 m² — no. (%)	439 (32.2)	473 (34.5)
Serum potassium — mmol/liter	4.3±0.4	4.3±0.4
Device therapy — no. (%)		
Implantable cardioverter–defibrillator	178 (13.0)	184 (13.4)
Cardiac-resynchronization therapy	38 (2.8)	22 (1.6)
Implantable cardioverter–defibrillator with cardiac resynchronization	74 (5.4)	99 (7.2)
Medication — no. (%)		
Diuretic	1150 (84.3)	1176 (85.7)
ACE inhibitor	1068 (78.3)	1057 (77.0)
ARB	262 (19.2)	267 (19.4)
ACE inhibitor, ARB, or both	1282 (94.0)	1275 (92.9)
Beta-blocker	1181 (86.6)	1193 (86.9)
Digitalis glycosides	363 (26.6)	377 (27.5)
Antiarrhythmic drug	196 (14.4)	192 (14.0)
Antithrombotic drug (antiplatelet or oral anticoagulant)	1205 (88.3)	1214 (88.4)
Lipid-lowering agent	857 (62.8)	856 (62.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. None of the characteristics differed significantly (P<0.05) between the two groups, except for diabetes mellitus (P=0.01) and cardiac-resynchronization therapy (P=0.04). To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, ECG electrocardiography, GFR glomerular filtration rate, and PCI percutaneous coronary intervention.
† Race was reported by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

group was 65.3%. Among the patients taking the study drug at 5 months, the mean (±SD) doses in the eplerenone and placebo groups, respectively, were 39.1±13.8 mg and 40.8±12.9 mg.

At the trial cutoff date, the study drug had been discontinued in 222 patients (16.3%) receiving eplerenone and 228 patients (16.6%) receiving placebo. Among these patients, the median time from randomization to the last dose was 533 days for eplerenone and 494 days for placebo.

At the trial cutoff date, 17 patients (1.2%) in the eplerenone group and 15 patients (1.1%) in the placebo group were lost to follow-up. If contact could not be made at the trial cutoff date, the data were censored in the analysis at the time of the last contact. The median duration of follow-up among all patients was 21 months, with 4783 patient-years of follow-up.

STUDY OUTCOMES

Death from cardiovascular causes or hospitalization for heart failure (the primary outcome) occurred in 249 patients (18.3%) in the eplerenone group and 356 patients (25.9%) in the placebo group (Fig. 1A and Table 2). The hazard ratio for the primary outcome in the eplerenone group, as compared with the placebo group, was 0.63 (95% confidence interval [CI], 0.54 to 0.74; P<0.001). The effect of eplerenone on this outcome was consistent in an unadjusted analysis (hazard ratio, 0.66; 95% CI, 0.56 to 0.78; P<0.001) (Table 2). It was also consistent across all prespecified subgroups (Fig. 2).

Death from any cause or hospitalization for heart failure occurred in 270 patients (19.8%) in the eplerenone group as compared with 376 patients (27.4%) in the placebo group (hazard ratio, 0.65; 95% CI, 0.55 to 0.76; P<0.001) (Table 2). A
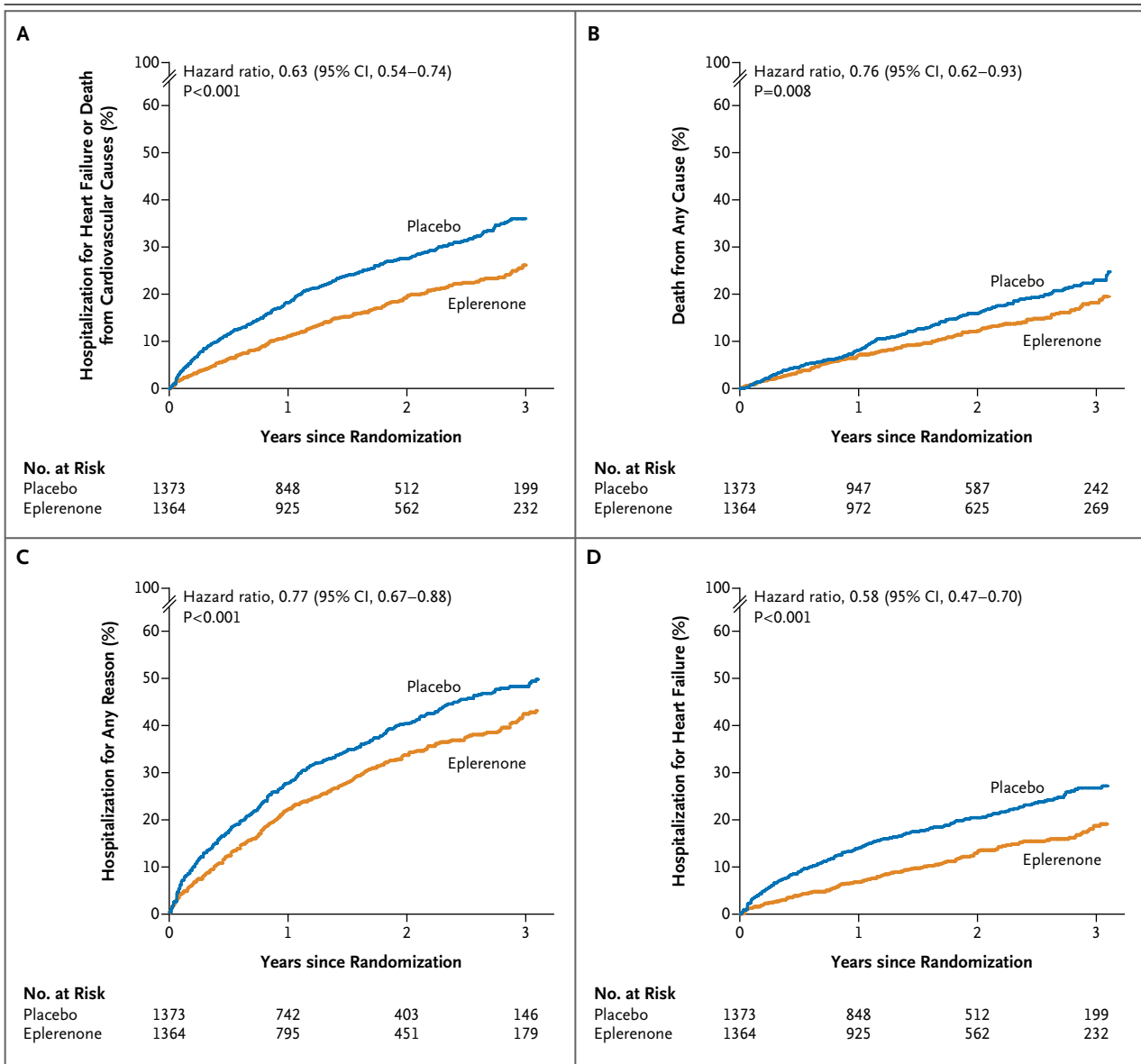
Figure 1. Cumulative Kaplan–Meier Estimates of Rates of the Primary Outcome and Other Outcomes, According to Study Group.

The hazard ratios for eplerenone versus placebo are shown for hospitalization for heart failure or death from cardiovascular causes (the primary outcome) (Panel A), death from any cause (Panel B), hospitalization for any reason (Panel C), and hospitalization for heart failure (Panel D).

total of 171 patients (12.5%) in the eplerenone group and 213 patients (15.5%) in the placebo group died (hazard ratio, 0.76; 95% CI, 0.62 to 0.93; P=0.008) (Fig. 1B and Table 2). A total of 147 deaths (10.8%) in the eplerenone group and 185 (13.5%) in the placebo group were attributed to cardiovascular causes (hazard ratio, 0.76; 95% CI, 0.61 to 0.94; P=0.01) (Table 2).

In the eplerenone group, 408 patients (29.9%) were hospitalized for any reason, as compared with 491 (35.8%) patients in the placebo group (hazard ratio, 0.77; 95% CI, 0.67 to 0.88; P<0.001) (Fig. 1C and Table 2). Of the patients receiving eplerenone, 164 (12.0%) were hospitalized for heart failure, as compared with 253 patients (18.4%) receiving placebo (hazard ratio, 0.58; 95% CI, 0.47 to 0.70; P<0.001) (Fig. 1D and Table 2). The total number of hospitalizations (includ-

Table 2. Primary Outcome, Component Events, and Key Secondary Outcomes.*

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Adjusted Hazard Ratio (95% CI)	Adjusted P Value	Unadjusted Hazard Ratio (95% CI)	Unadjusted P Value
	no. of patients (%)					
Primary outcome: death from cardiovascular causes or hospitalization for heart failure	249 (18.3)	356 (25.9)	0.63 (0.54–0.74)	<0.001	0.66 (0.56–0.78)	<0.001
Prespecified adjudicated secondary outcomes						
Death from any cause or hospitalization for heart failure	270 (19.8)	376 (27.4)	0.65 (0.55–0.76)	<0.001	0.68 (0.58–0.79)	<0.001
Death from any cause	171 (12.5)	213 (15.5)	0.76 (0.62–0.93)	0.008	0.78 (0.64–0.95)	0.01
Death from cardiovascular causes	147 (10.8)	185 (13.5)	0.76 (0.61–0.94)	0.01	0.77 (0.62–0.96)	0.02
Hospitalization for any reason	408 (29.9)	491 (35.8)	0.77 (0.67–0.88)	<0.001	0.78 (0.69–0.89)	<0.001
Hospitalization for heart failure	164 (12.0)	253 (18.4)	0.58 (0.47–0.70)	<0.001	0.61 (0.50–0.75)	<0.001
Hospitalization for cardiovascular causes	304 (22.3)	399 (29.1)	0.69 (0.60–0.81)	<0.001	0.72 (0.62–0.83)	<0.001
Fatal or nonfatal myocardial infarction	45 (3.3)	33 (2.4)	1.32 (0.84–2.06)	0.23	1.34 (0.86–2.10)	0.20
Death from any cause or hospitalization for any reason	462 (33.9)	569 (41.4)	0.75 (0.66–0.85)	<0.001	0.76 (0.68–0.86)	<0.001
Death from heart failure or hospitalization for heart failure	170 (12.5)	262 (19.1)	0.58 (0.48–0.70)	<0.001	0.61 (0.51–0.74)	<0.001
Fatal or nonfatal stroke	21 (1.5)	26 (1.9)	0.79 (0.44–1.41)	0.42	0.78 (0.44–1.39)	0.40
Implantation of a cardioverter–defibrillator	61 (4.5)	59 (4.3)	0.99 (0.69–1.42)	0.98	1.01 (0.71–1.45)	0.95
Implantation of a cardiac-resynchronization device	33 (2.4)	41 (3.0)	0.77 (0.49–1.22)	0.27	0.78 (0.49–1.23)	0.28
Hospitalization for worsening renal function†	9 (0.7)	8 (0.6)	0.97 (0.37–2.58)	0.95	1.09 (0.42–2.82)	0.86
Hospitalization for hyperkalemia†	4 (0.3)	3 (0.2)	1.15 (0.25–5.31)	0.85	1.31 (0.29–5.87)	0.72
Other outcomes‡						
Sudden cardiac death	60 (4.4)	76 (5.5)	0.76 (0.54–1.07)	0.12	0.77 (0.55–1.08)	0.12
Death from worsening heart failure	45 (3.3)	61 (4.4)	0.68 (0.46–1.00)	0.05	0.71 (0.48–1.04)	0.08

* Adjusted results were adjusted for prespecified baseline characteristics (see the Statistical Analysis section). CI denotes confidence interval.
† No death was attributed to hospitalization for worsening renal function or hyperkalemia.
‡ "Other outcomes" were secondary outcomes that were adjudicated but not prespecified.

ing second and subsequent hospitalizations) was also lower in the eplerenone group (750, vs. 961 in the placebo group, for a 24% reduction; P<0.001), as were the total numbers of hospitalizations for cardiovascular reasons (509 vs. 699, for a 29% reduction; P<0.001) and hospitalizations for heart failure (273 vs. 429, for a 38% reduction; P<0.001). Findings for all other prespecified adjudicated secondary outcomes and other outcomes are summarized in Table 2, in which all the results are adjusted for prespecified baseline variables.

The estimated number of patients who would need to be treated to prevent one primary outcome from occurring, per year of follow up, was

19 (95% CI, 15 to 27), and the estimated number needed to treat to postpone one death, per year of follow up, was 51 (95% CI, 32 to 180).

SAFETY

During the course of the study, 188 patients (13.8%) receiving eplerenone and 222 patients (16.2%) receiving placebo discontinued the study drug because of an adverse event (P=0.09). Relevant adverse events are summarized in Table 3.

At 1 month, the mean change in serum creatinine level from baseline was 0.15±0.35 mg per deciliter (13.3±30.9 μmol per liter) in the eplerenone group, as compared with 0.07±0.29 mg per deciliter (6.2±25.6 μmol per liter) in the placebo

group. At the trial cutoff date, the serum creatinine level had increased from baseline by 0.09±0.37 mg per deciliter (8.0±32.7μmol per liter) and 0.04±0.40 (3.5±35.4 μmol per liter), respectively.

At 1 month, the mean change in potassium level from baseline was 0.16±0.51 mmol per liter in the eplerenone group, as compared with 0.04±1.16 mmol per liter in the placebo group (P=0.001). At the trial cutoff date, potassium levels had increased from baseline by 0.16±0.56 and 0.05±0.53 mmol per liter, respectively (P<0.001 for both comparisons). A serum potassium level above 5.5 mmol per liter was reported in 158 of 1336 patients (11.8%) in the eplerenone group and 96 of 1340 patients (7.2%) in the placebo group (P<0.001). A serum potassium level above 6.0 mmol per liter occurred in 33 of 1336 patients (2.5%) in the eplerenone group and 25 of 1340 patients (1.9%) in the placebo group (P=0.29). A serum potassium level below 4.0 mmol per liter was reported in 519 of 1336 patients (38.8%) in the eplerenone group and 648 of 1340 patients (48.4%) in the placebo group (P<0.001). A serum potassium level below 3.5 mmol per liter was reported in 100 of 1336 patients (7.5%) in the eplerenone group and 148 of 1340 patients (11.0%) in the placebo group (P=0.002).

Systolic blood pressure decreased during the study period to a greater degree in the eplerenone group, with a mean overall reduction of 2.5±17.9 mm Hg, than in the placebo group, with a reduction of 0.3±17.2 mm Hg (P=0.001). There were no other clinically significant differences between the two groups with respect to laboratory variables, reported adverse events, or adverse events leading to permanent withdrawal of the study drug.

DISCUSSION

We evaluated the effect of adding eplerenone to recommended treatment for systolic heart failure in patients with mild symptoms (NYHA functional class II symptoms). The rate of the primary outcome, a composite of death from cardiovascular causes or hospitalization for heart failure, was 18.3% in the eplerenone group versus 25.9% in the placebo group. This effect of eplerenone was consistent across all prespecified subgroups. With eplerenone, there was also a reduction in

Figure 2 (facing page). Hazard Ratios for Hospitalization for Heart Failure or Death from Cardiovascular Causes (the Primary Outcome) with Eplerenone versus Placebo, According to Prespecified Subgroups.

The subgroups are based on baseline demographic and clinical characteristics. The size of the square corresponds to the number of patients with an event. Data are missing for some patients in some subgroups. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, BNP B-type natriuretic peptide, CRT cardiac-resynchronization therapy, GFR glomerular filtration rate, ICD implantable cardioverter–defibrillator, and LVEF left ventricular ejection fraction.

both the rate of death from any cause and the rate of hospitalization for any reason.

The mechanisms by which mineralocorticoid-receptor antagonists such as eplerenone provide cardiovascular protection in patients with heart failure are not completely understood. Activation of the mineralocorticoid receptor by both aldosterone and cortisol plays an important role in the pathophysiology of heart failure,[1,9] and mineralocorticoid receptors are overexpressed in the failing heart.[10,11] Despite therapy with ACE inhibitors, ARBs, and beta-blockers, patients with even mild heart failure may have persistently elevated plasma aldosterone and cortisol levels.[12-17] Mineralocorticoid receptors are not blocked by these treatments.

Activation of the mineralocorticoid receptor has been shown to promote cardiac fibrosis in experimental models.[18] In patients with heart failure,[19] as well as in patients after myocardial infarction, the use of mineralocorticoid-receptor antagonists decreases extracellular-matrix turnover, as assessed by measuring serum levels of collagen biomarkers.[20,21] Experimental and clinical studies suggest that mineralocorticoid-receptor antagonists favorably affect several other important mechanisms known to have a role in the progression of heart failure.[1,15,22,23]

In our study, as anticipated, there was an increased incidence of hyperkalemia among patients receiving eplerenone. This finding underscores the need to measure serum potassium levels serially and to adjust the dose of eplerenone accordingly. We attempted to minimize the risk of hyperkalemia by excluding patients with a baseline serum potassium level above 5.0 mmol per liter and a baseline estimated GFR below 30 ml per minute per 1.73 m².
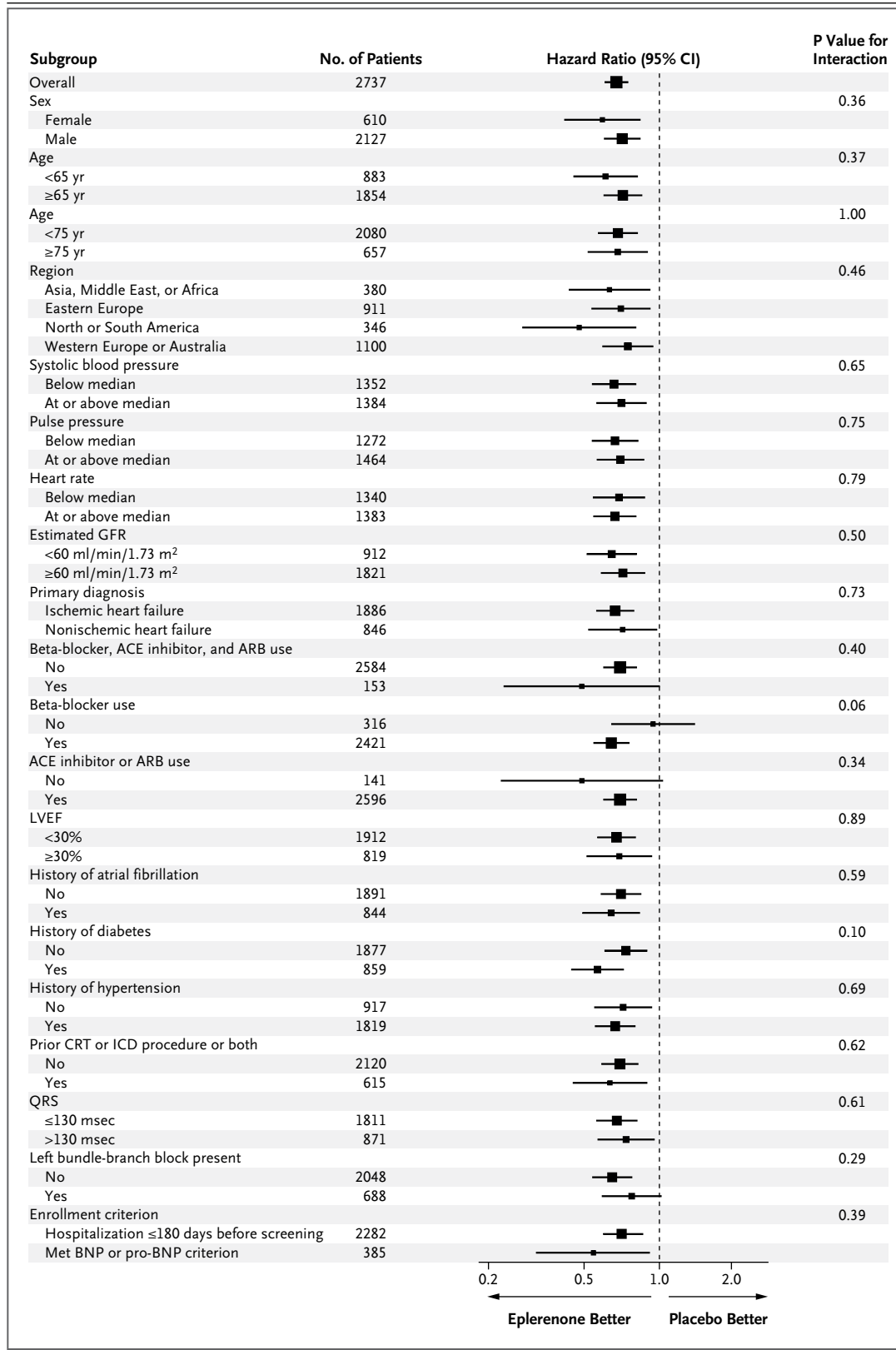
Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Overall	2737		
Sex			0.36
Female	610		
Male	2127		
Age			0.37
<65 yr	883		
≥65 yr	1854		
Age			1.00
<75 yr	2080		
≥75 yr	657		
Region			0.46
Asia, Middle East, or Africa	380		
Eastern Europe	911		
North or South America	346		
Western Europe or Australia	1100		
Systolic blood pressure			0.65
Below median	1352		
At or above median	1384		
Pulse pressure			0.75
Below median	1272		
At or above median	1464		
Heart rate			0.79
Below median	1340		
At or above median	1383		
Estimated GFR			0.50
<60 ml/min/1.73 m^2	912		
≥60 ml/min/1.73 m^2	1821		
Primary diagnosis			0.73
Ischemic heart failure	1886		
Nonischemic heart failure	846		
Beta-blocker, ACE inhibitor, and ARB use			0.40
No	2584		
Yes	153		
Beta-blocker use			0.06
No	316		
Yes	2421		
ACE inhibitor or ARB use			0.34
No	141		
Yes	2596		
LVEF			0.89
<30%	1912		
≥30%	819		
History of atrial fibrillation			0.59
No	1891		
Yes	844		
History of diabetes			0.10
No	1877		
Yes	859		
History of hypertension			0.69
No	917		
Yes	1819		
Prior CRT or ICD procedure or both			0.62
No	2120		
Yes	615		
QRS			0.61
≤130 msec	1811		
>130 msec	871		
Left bundle-branch block present			0.29
No	2048		
Yes	688		
Enrollment criterion			0.39
Hospitalization ≤180 days before screening	2282		
Met BNP or pro-BNP criterion	385		

Hazard Ratio axis: 0.2 0.5 1.0 2.0

Eplerenone Better ← | → Placebo Better

Table 3. Selected Investigator-Reported Adverse Events and Those Leading to Permanent Withdrawal of the Study Drug, According to Study Group.*

Event	Adverse Event			Adverse Event Leading to Study-Drug Withdrawal		
	Eplerenone (N=1360)	Placebo (N=1369)	P Value	Eplerenone (N=1360)	Placebo (N=1369)	P Value
	no. of patients (%)			*no. of patients (%)*		
All events	979 (72.0)	1007 (73.6)	0.37	188 (13.8)	222 (16.2)	0.09
Hyperkalemia	109 (8.0)	50 (3.7)	<0.001	15 (1.1)	12 (0.9)	0.57
Hypokalemia	16 (1.2)	30 (2.2)	0.05	0	3 (0.2)	0.25
Renal failure	26 (1.9)	32 (2.3)	0.51	4 (0.3)	6 (0.4)	0.75
Hypotension	46 (3.4)	37 (2.7)	0.32	0	3 (0.2)	0.25
Gynecomastia or other breast disorders	10 (0.7)	14 (1.0)	0.54	2 (0.1)	2 (0.1)	1.00

* Patients who had received at least one dose of the study drug were included in the safety analysis. P values were calculated on the basis of the number of patients.

In contrast, the risk of hypokalemia was significantly reduced among patients receiving eplerenone. This is important because a serum potassium level below 4.0 mmol per liter has been associated with an increased risk of death from any cause among patients with systolic heart failure.[22]

Our study has some limitations. Our results may not be applicable to all patients with mild symptoms, because to be eligible for the study, patients had to have additional factors known to increase cardiovascular risk, including an age over 55 years, in most cases an ejection fraction of no more than 30%, and a recent hospitalization for a cardiovascular reason. Use of an implantable cardioverter–defibrillator was relatively infrequent, but this finding is similar to those in recent registries and trials.[24,25] The early stopping of the trial may have resulted in overestimation of the magnitude of the treatment effect,[26] but the results are consistent with those seen in RALES.[2]

In conclusion, our study showed that, as compared with placebo, eplerenone added to recommended therapy for systolic heart failure in patients with mild symptoms was associated with a reduction in the rate of death from a cardiovascular cause or hospitalization for heart failure. Similar reductions were seen in rates of death from any cause, death from cardiovascular causes, hospitalization for any reason, and hospitalization for heart failure.

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