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History of Hypertension and the Effects of Eplerenone in Patients with Acute Myocardial Infarction Complicated by Systolic Heart Failure

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Abstract

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (n=6632), eplerenone-associated reduction in all-cause mortality was significantly greater in those with a history of hypertension (Hx-HTN). There were 4007 patients with Hx-HTN (eplerenone: n=1983) and 2625 patients without Hx-HTN (eplerenone: n=1336). Propensity scores for eplerenone use, separately calculated for patients with and without Hx-HTN, were used to assemble matched cohorts of 1838 and 1176 pairs of patients. In patients with Hx-HTN, all-cause mortality occurred in 18% of patients treated with placebo (rate, 1430/10 000 person-years) and 14% of patients treated with eplerenone (rate, 1058/10 000 person-years) during 2350 and 2457 years of follow-up, respectively (hazard ratio [HR]: 0.71; 95% CI: 0.59 to 0.85; P<0.0001). Composite end point of cardiovascular hospitalization or cardiovascular mortality occurred in 33% of placebo-treated patients (3029/10 000 person-years) and 28% of eplerenone-treated patients (2438/10 000 person-years) with Hx-HTN (HR: 0.82; 95% CI: 0.72 to 0.94; P=0.003). In patients without Hx-HTN, eplerenone reduced heart failure hospitalization (HR: 0.73; 95% CI: 0.55 to 0.97; P=0.028) but had no effect on mortality (HR: 0.91; 95% CI: 0.72 to 1.15; P=0.435) or on the composite end point (HR: 0.91; 95% CI: 0.76 to 1.10; P=0.331). Eplerenone should, therefore, be prescribed to all of the post–acute myocardial infarction patients with reduced left ventricular ejection fraction and heart failure regardless of Hx-HTN.

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Author Contributions

Bertram Pitt conceived the study hypothesis for this subanalysis of EPHESUS. Ali Ahmed developed the subanalysis design, and wrote the first draft of the manuscript. Ali Ahmed conducted statistical analyses in consultation with Thomas Love. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. Ali Ahmed had full access to the data.

Keywords

Eplerenone; hypertension; myocardial infarction; heart failure; morbidity; mortality

Introduction

In the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS), eplerenone, a selective aldosterone blocker, significantly reduced all-cause mortality and the coprimary combined end points of cardiovascular (CV) hospitalization or CV mortality.1 A subgroup analysis of the EPHESUS suggested that the effect of eplerenone on all-cause mortality was greater in patients with a history of hypertension (Hx-HTN) than in those without Hx-HTN (P for interaction=0.05).1 However, there was no significant difference between these groups for eplerenone on the coprimary combined end points of CV hospitalization or CV mortality. To gain further insight into this relationship, we examined the effects of eplerenone on mortality and morbidity in a propensity score–matched cohort of patients with and without Hx-HTN.

Methods

Study Design and Patients

EPHESUS was a multicenter, international, randomized, double-blind, placebo-controlled clinical trial of eplerenone.1 Briefly, 6632 patients with acute myocardial infarction (AMI) complicated by low (≤40%) left ventricular ejection fraction (LVEF) and symptomatic heart failure (HF) were randomly assigned within 3 to 14 days of their AMI to receive eplerenone 25 mg/d titrated to 50 mg/d (n=3319) or matching placebo (n=3313). Patients were receiving standard medical therapy, including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (87%) and a beta-blocker. Patients were followed for up to 2.5 years, with a mean follow-up of 16 months. Patients in the placebo and eplerenone groups were receiving a mean dose of 43.5 mg and 42.6 mg per day, respectively. Exclusion criteria included the use of potassium-sparing diuretics, a serum creatinine concentration >2.5 mg/dL (220 μmol/L), and a serum potassium concentration >5.0 mEq/L (mmol/L). Of the EPHESUS participants, 4007 patients had a history of hypertension (Hx-HTN), and 2625 had no Hx-HTN at the time of enrollment. Of the 4007 patients with Hx-HTN, 2024 (50.5%) were in the placebo group, and 1983 (49.5%) were in the eplerenone group. Of the 2625 patients without Hx-HTN, 1289 (49.1%) were in the placebo group, and 1336 (50.9%) were in the eplerenone group.

The two primary end points of the EPHESUS, all-cause mortality and the combined end point of CV hospitalization or CV mortality, were also the primary end points for this analysis. Major secondary end points from EPHESUS, such as CV mortality, which included mortality because of AMI, HF, stroke, and sudden cardiac death (SCD), as well as hospitalization because of AMI and HF, were also studied. The cause of death or the primary diagnosis leading to hospitalization was adjudicated by a blinded EPHESUS critical events committee.

Statistical Analysis

Because the balance achieved by randomization in the main trial may have been lost in the groups with and without Hx-HTN, propensity scores for the receipt of eplerenone were used to assemble a balanced cohort. The propensity score for the receipt of eplerenone for a patient is defined as the conditional probability of receiving eplerenone given that patient's measured covariates.2–6 Propensity scores were calculated separately for each of the 4007

and 2625 patients with and without Hx-HTN, respectively, using a nonparsimonious multivariable logistic regression model, incorporating the 36 baseline covariates (Table 1). Patients receiving eplerenone and placebo were matched based on their propensity to receive eplerenone. In all, 1838 pairs of patients with Hx-HTN and 1176 pairs of patients without Hx-HTN were matched. Absolute standardized differences were estimated to assess residual balance after matching.6,7

We used Kaplan–Meier plots and matched Cox regression analysis to estimate the effect of eplerenone in patients with and without Hx-HTN. We used multivariable Cox regression analyses in the prematch cohort, separately adjusting for the raw propensity scores. All of the analyses were based on intent to treat. All of the statistical tests were evaluated using 2-tailed 95% CIs.

Because the sample size of matched patients with Hx-HTN (n=3676) was larger than matched patients without Hx-HTN (n=2352), we conducted a sensitivity analysis by repeating our analysis in a smaller group of patients with Hx-HTN. In addition, we conducted a sensitivity analysis to determine the potential effects of an unmeasured covariate that may potentially invalidate our main conclusions.6,8,9

Results

Study Patients

Baseline characteristics of patients with and without Hx-HTN are presented in Table 1. In both groups with and without Hx-HTN, the distribution of all of the measured baseline covariates was balanced, and there were no statistically significant differences between treatment groups.

Eplerenone and All-Cause Mortality

During a median follow-up of 16 months, 596 matched patients with Hx-HTN (16.2%) and 336 matched patients without Hx-HTN (14.3%) died of all causes. Among patients with Hx-HTN, all-cause mortality occurred in 18% of the placebo group and 14% of the eplerenone group (hazard ratio [HR]: 0.71; 95% CI: 0.59 to 0.85; P<0.0001; Figure 1A and Table 2). Among patients without Hx-HTN, all-cause mortality occurred in 14.4% of the placebo group and 14.2% of the eplerenone group (HR: 0.91; 95% CI: 0.72 to 1.15; P=0.435; Figure 1B and Table 2).

Eplerenone and CV Hospitalization or CV Mortality

Among patients with Hx-HTN, the coprimary combined end points of CV hospitalization or CV mortality occurred in 32.8% patients in the placebo group and 28.2% of patients in the eplerenone group (HR: 0.82; 95% CI: 0.72 to 0.94; P=0.003; Figure 2A and Table 2). Among patients without Hx-HTN, the coprimary combined end points of CV hospitalization or CV mortality occurred in 25.3% of patients in the placebo group and 23.6% of patients in the eplerenone group (HR: 0.91; 95% CI: 0.76 to 1.10; P=0.331; Figure 2B and Table 2).

Eplerenone, SCD, and Other Secondary Study End Points

SCD occurred in 6.5% of patients with Hx-HTN in the placebo group and 5.0% of patients with Hx-HTN in the eplerenone group (Figure 3A and Table 2). Among patients without Hx-HTN, SCD occurred in 5.2% patients in the placebo group and 4.4% patients in the eplerenone group (Figure 3B and Table 2). Effects of eplerenone on other secondary end points in patients with and without Hx-HTN are displayed in Table 2.

Eplerenone and Adverse Events

In patients with Hx-HTN, the incidence of severe hyperkalemia was significantly higher in patients receiving eplerenone (5.9% versus 4.2%; odds ratio for patients receiving eplerenone: 1.43; 95% CI: 1.06 to 1.93; P=0.019; Table 3). The incidence of severe hypokalemia was lower in patients receiving eplerenone (14.7% versus 9.6%; odds ratio for patients receiving eplerenone: 0.62; 95% CI: 0.51 to 0.76; P<0.0001). Other adverse events are displayed in Table 3.

Eplerenone, History of Hypertension and Baseline Blood Pressure

Eplerenone had a favorable effect on outcomes in patients with Hx-HTN regardless of their baseline systolic blood pressure (SBP). In the subgroups of patients with Hx-HTN and a baseline SBP of ≤120 mm Hg, all-cause mortality occurred in 191 placebo patients (rate: 1465/10 000 person-years) and 157 eplerenone patients (rate: 1176/10,000 person-years; HR: 0.80; 95% CI: 0.65 to 0.99; P=0.043). Eplerenone also reduced CV hospitalization or CV mortality (HR: 0.86; 95% CI: 0.73 to 0.997; P=0.046) in these patients. In Hx-HTN patients with a baseline SBP of >120 mm Hg, similarly, eplerenone reduced both all-cause mortality (HR: 0.68; 95% CI: 0.52 to 0.87; P=0.002) and the coprimary composite end point (HR: 0.79; 95% CI: 0.66 to 0.94; P=0.010).

Eplerenone and Changes in Baseline Blood Pressure

Increases in SBP from baseline (Table 1) were similar in both groups of patients with or without Hx-HTN and were slightly greater in the placebo group. The SBP increased by 6 and 3 mm Hg in the placebo and eplerenone patients, respectively, in both groups with and without Hx-HTN.

Results of Sensitivity Analyses

Because the group with Hx-HTN (n=3676) was larger than the group without Hx-HTN (n=2352), we assembled a cohort of patients with Hx-HTN that was similar in size to that of those without Hx-HTN (please see the data supplement, available online at http://hyper.ahajournals.org). In this smaller group of patients with Hx-HTN (n=2334), we observed that eplerenone use was associated with reduction in all-cause mortality (HR: 0.76; 95% CI: 0.61 to 0.95; P=0.014).

Within the Hx-HTN–matched cohort, sign-score tests for matched survival data with censoring provide evidence that the use of eplerenone, compared with placebo, was associated with decreased all-cause mortality (z=3.73; 2-tailed, P=0.0002) and decreased rates of CV hospitalization or CV mortality (z=2.92; P=0.0035). Sensitivity analyses suggest that an unmeasured binary covariate would need to increase the odds of eplerenone use by >17.6% to explain the all-cause mortality association and by >6.6% to explain the association with the coprimary end points.

Discussion

The results of this analysis demonstrate that the use of eplerenone in patients with Hx-HTN within 3 to 14 days of an AMI, complicated by reduced LVEF and symptomatic HF, was associated with significant reductions in all-cause mortality and the coprimary end points of CV hospitalization or CV mortality. In addition, the use of eplerenone was associated with a significant reduction in SCD in these patients. Although the direction of change with eplerenone in the subgroup of patients without Hx-HTN was similar, significant reductions in these end points were not observed in this subgroup; however, in patients without Hx-HTN, eplerenone significantly reduced hospitalization for HF, suggesting a long-term effect on ventricular remodeling. Although approximately two thirds of patients in EPHESUS had

Hx-HTN, their mean blood pressure at the time of random assignment post-AMI was within normal limits

There are several plausible explanations for the differential benefit of eplerenone in patients with Hx-HTN. Effects of a treatment on outcomes are known to vary between groups of patients based on differences in pathophysiology, natural history, severity of disease, comorbidity, and absolute risks between groups.10 EPHESUS patients with Hx-HTN were older and had more severe disease and comorbidity burden than those without Hx-HTN. They had 14% greater risk for all-cause mortality and 28% increased risk for CV mortality or CV hospitalizations than those without Hx-HTN. Pathophysiologically, compared with patients without Hx-HTN, those with Hx-HTN are at an increased risk of incident AMI, subsequent ventricular remodeling, and CV mortality.11–14

Hypertension predisposes patients to an increase in reactive oxygen species, vascular remodeling, and myocardial collagen formation.15–18 After AMI, patients with Hx-HTN have been found to have a greater degree of ventricular remodeling than those without Hx-HTN.13,19,20 Ventricular remodeling results in myocardial stretch, which is an important stimulus for activation of various neurohormones, including angiotensin II and aldosterone.21,22 HF is associated with an upregulation of mineralocorticoid receptors and aldosterone with an increase in myocardial calcium channel expression.23–26 Recently, AMI has been shown to cause electric remodeling before mechanical remodeling and LV hypertrophy.27 The increase in intracellular calcium associated with electrical remodeling has been suggested to increase the risk of ventricular arrhythmias and SCD.28,29 Alterations in intracellular calcium and potassium may be greater in patients with AMI and Hx-HTN, many of whom have LV hypertrophy, and an increase in mineralocorticoid receptors and calcium channel expression.25,26 Therefore, the effectiveness of eplerenone in patients with Hx-HTN, most of whom were treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a 13-adrenergic receptor blocker, in reducing total mortality and SCD along with a trend toward a reduction in death because of progressive HF can be explained by the effects of aldosterone blockade in preventing electric remodeling, as well as by improving sympathetic/parasympathetic balance related to a decrease in reactive oxygen species production and an improvement in NO availability.[30–33] These effects are in addition to the effects of eplerenone on ventricular mechanical remodeling, LV hypertrophy, and collagen formation, all of which are likely of greater magnitude in those with Hx-HTN.34–38

Results of our subgroup analysis suggest that the effects of eplerenone were observed regardless of baseline SBP, suggesting a long-term effect of HTN on target organs rather than baseline blood pressure levels as the underlying mechanistic explanation for the differential effect of eplerenone in the group with Hx-HTN. Another plausible explanation of a differential benefit of eplerenone in patients with Hx-HTN is the larger sample of these patients; however, sensitivity analysis suggests that eplerenone was beneficial in a smaller subset of patients with Hx-HTN. In addition, statistical analysis showed no significant difference in the treatment effect of eplerenone on SBP between patients with and without Hx-HTN, suggesting that our findings were not driven by higher absolute reductions in SBP among patients with Hx-HTN.

This analysis suggests that patients with AMI complicated by a low LVEF and symptomatic HF should be risk-stratified based on Hx-HTN. Those with Hx-HTN should be prescribed eplerenone to improve outcomes. Although we did not observe a significant effect of eplerenone on mortality in patients without Hx-HTN, we did observe a significant reduction in HF hospitalization, likely mediated by a reduction in ventricular remodeling. There was a trend toward a reduction in mortality, but analysis of this subgroup may have been

underpowered to detect a significant difference in mortality and other outcomes, which is not surprising given the low baseline risk in these patients.11 Reduction in HF hospitalization would suggest a long-term effect of eplerenone on mortality in these patients.

Eplerenone was well tolerated in patients with and without Hx-HTN. Although more patients receiving eplerenone experienced hyperkalemia (>6 mEq/L), overall absolute rates were low, and no deaths were attributed to hyperkalemia in patients receiving eplerenone. Patients receiving eplerenone had a lower risk of developing hypokalemia (<3.5 mEq/L). This is important, because the overall absolute rate of hypokalemia was higher than that of hyperkalemia, which has been associated with increased mortality.39–42

Perspectives

This analysis suggests that patients with AMI, reduced LVEF, and symptomatic HF should be risk stratified based on their Hx-HTN; and those with Hx-HTN should be treated early post-AMI with eplerenone to prevent death, especially SCD. Because HF hospitalization is an important predictor of CV death and eplerenone reduced HF hospitalization in patients without Hx-HTN, eplerenone should also be initiated in these patients

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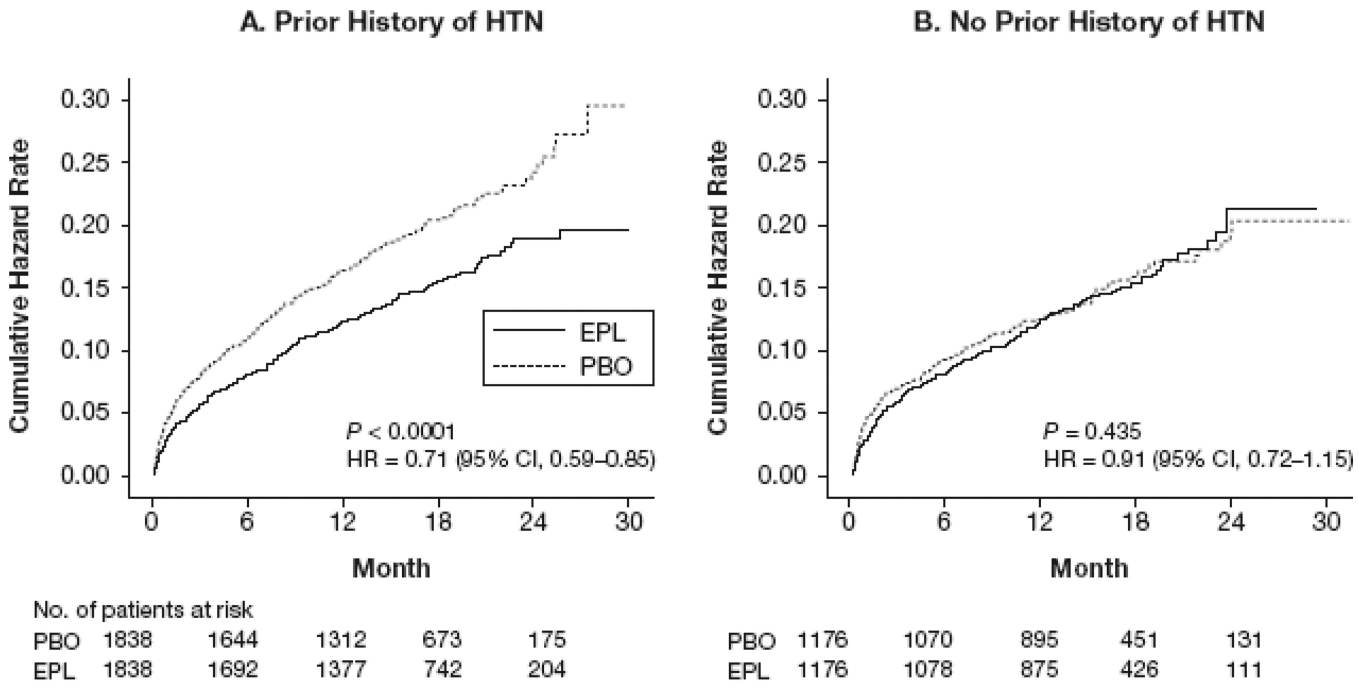
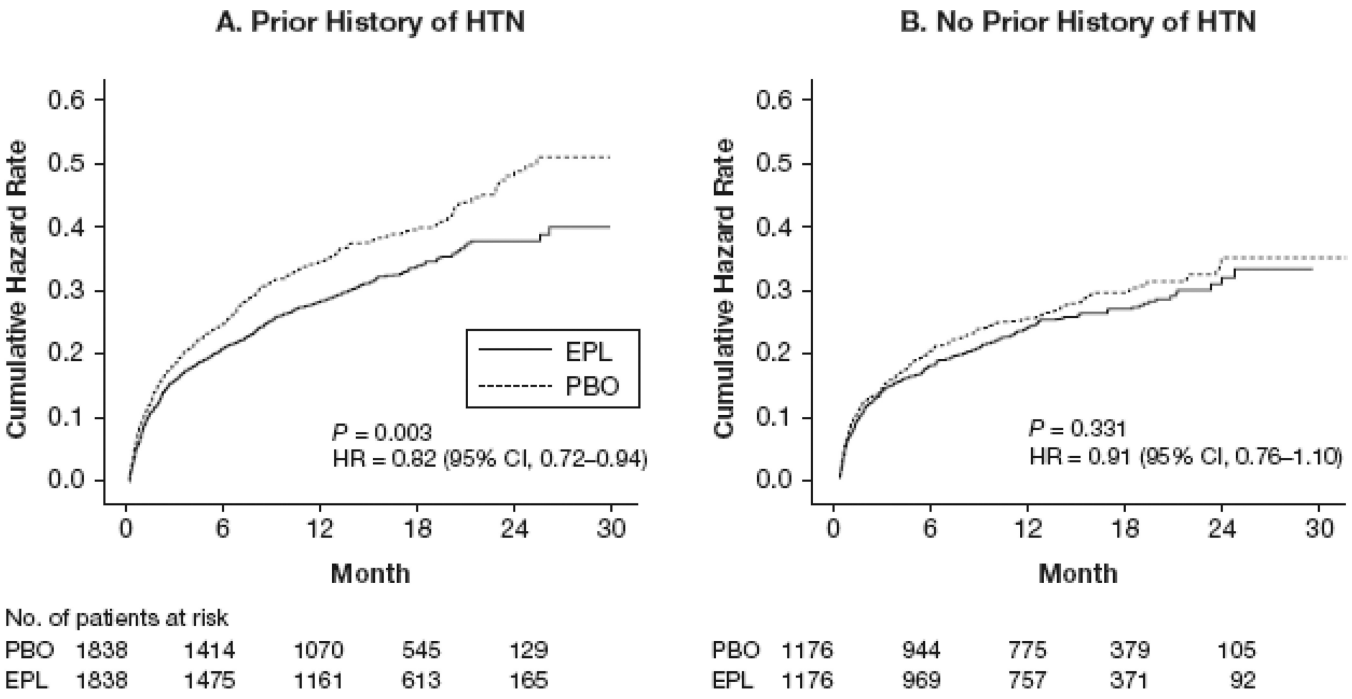


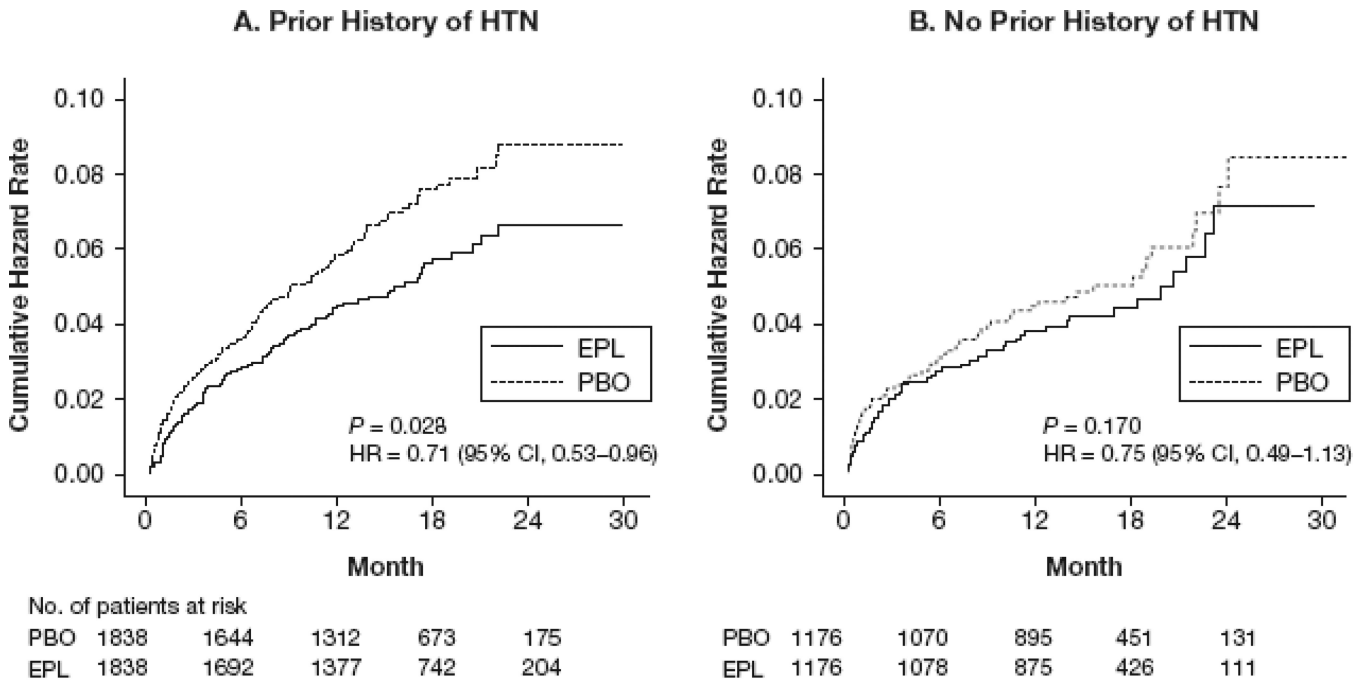
CI indicates confidence interval; EPL, eplerenone; HR, hazard ratio; HTN, hypertension; PBO, placebo.

Figure 1.
Kaplan-Meier plots for all-cause mortality in patients (a) with and (b) without Hx-HTN.



CI indicates confidence interval; EPL, eplerenone; HR, hazard ratio; HTN, hypertension; PBO, placebo.

Figure 2.
Kaplan-Meier plots for co-primary combined end point of cardiovascular (CV) hospitalization or CV mortality in patients (a) with and (b) without Hx-HTN.



CI indicates confidence interval; EPL, eplerenone; HR, hazard ratio; HTN, hypertension; PBO, placebo.

Figure 3.
Kaplan-Meier plots for sudden cardiac death in patients (a) with and (b) without Hx-HTN.

TABLE 1

Baseline patient characteristics of propensity score matched patients

Characteristics n (%) or mean (±SD)	History of hypertension			No history of hypertension		
	Placebo (n=1838)	Eplerenone (n=1838)	*P* value	Placebo (n=1176)	Eplerenone (n=1176)	*P* value
Age, y *	65.5 (±11)	65.4 (±11)	0.654	61.7 (±13)	61.8 (±12)	0.859
Age ≥65 y *	1032 (56)	1010 (55)	0.486	500 (43)	502 (42)	0.934
Women *	634 (35)	623 (24)	0.702	248 (21)	244 (21)	0.879
Nonwhites	177 (10)	185 (10)	0.698	115 (10)	119 (9)	0.674
Smoking status *						
Current	453 (25)	461 (25)	0.895	471 (40)	464 (40)	0.957
Never	836 (46)	822 (45)		354 (30)	357 (30)	
Former	549 (30)	555 (30)		351 (30)	355 (30	
Medical history						
AMI *	545 (30)	543 (30)	0.971	277 (24)	278 (23)	1.000
Angina *	881 (48)	893 (49)	0.717	357 (30)	363 (21)	0.823
HF *	322 (18)	319 (17)	0.896	117 (10)	119 (10)	0.891
Prior HF hospitalization *	161 (9)	159(9)	0.953	68 (6)	66 (6)	0.859
Diabetes *	685 (37)	689 (38)	0.919	288 (25)	288 (25)	1.000
Killip status *						
I	294 (16)	308 (17)	0.928	179 (15)	174 (15)	0.964
II	1157 (63)	1152 (63)		790 (67)	799 (68)	
III	332 (18)	323 (18)		167 (14)	161 (14)	
IV	55 (3)	55 (3)		40 (3)	42 (4)	
Medications						
ACEIs *	1584 (86)	1585 (86)	1.000	966 (82)	964 (82)	0.957
ARBs	60 (3)	63 (3)	0.855	32 (3)	32 (3)	1.000
Beta-blockers	1364 (74)	1370 (75)	0.850	886 (75)	886 (75)	1.000

Characteristics n (%) or mean (±SD)	History of hypertension			No history of hypertension		
	Placebo (n=1838)	Eplerenone (n=1838)	*P* value	Placebo (n=1176)	Eplerenone (n=1176)	*P* value
Alpha-blockers *	49 (3)	46 (3)	0.757	8 (1)	7 (1)	0.803
Calcium channel blockers *	356 (19)	356 (19)	1.000	127 (11)	128 (11)	1.000
Glycoprotein IIb/IIIa blockers	14 (1)	18 (1)	0.595	10 (1)	10 (1)	1.000
Antiarrhythmic drugs	230 (13)	221 (12)	0.651	126 (11)	129 (11)	0.843
Antiplatelet drugs *	464 (25)	469 (26)	0.880	402 (34)	394 (34)	0.760
Anticoagulants *	339 (18)	327 (18)	0.638	173 (15)	171 (15)	0.953
Aspirin	1640 (89)	1640 (89)	1.000	1037 (88)	1039 (88)	0.949
Statins *	798 (43)	809 (44)	0.740	595 (51)	596 (51)	0.997
Other lipid-lowering agents	31 (2)	34 (2)	0.803	16 (1)	16 (1)	1.000
Digoxin †	296 (16)	290 (16)	0.787	159 (14)	160 (14)	0.952
Nitrates *	1232 (67)	1223 (67)	0.753	651 (55)	652 (55)	1.000
Loop diuretics *	1069 (58)	1068 (58)	1.000	593 (50)	595 (51)	0.967
Other diuretics *	176 (10)	168 (9)	0.692	66 (6)	65 (6)	1.000
Potassium supplements	322 (18)	309 (17)	0.570	180 (15)	180 (15)	1.000
Magnesium supplements	77 (4)	76 (4)	1.000	40 (3)	36 (3)	0.643
Body mass index, kg/m^2 *	28 (±5)	28 (±4)	0.812	27 (±4)	26 (±4)	0.738
Blood pressure, mm Hg						
Systolic *	123 (±17)	123 (±17)	0.894	114 (±14)	113 (±15)	0.795
Diastolic *	74 (±11)	74 (±11)	0.997	70 (±10)	70 (±10)	0.934
Heart rate per minute	74 (±11)	74 (±11)	0.762	75 (±12)	75 (±12)	0.822
LVEF, % †	33 (±6)	33 (±6)	0.767	33 (±6)	33 (±6)	0.735
Serum concentrations, mean						
Sodium, mmol/L *	140 (±4)	140 (±5)	0.850	139 (±4)	139 (±4)	0.610
Potassium, mmol/L *	4.3 (±0.5)	4.3 (±0.5)	0.949	4.3 (±0.4)	4.3 (±0.4)	0.567
Creatinine, mg/dL *	1.16 (±0.4)	1.15 (±0.3)	0.784	1.09 (±0.4)	1.09 (±0.3)	0.949

* indicates $P<0.0001$;

† $P<0.05$ for significant difference between patients with and without a history of hypertension.

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; HF, heart failure, LVEF, left ventricular ejection fraction.

TABLE 2

Effects of Eplerenone on Primary and Secondary End Points

History of hypertension					
Primary end points	**Rate, per 10,000 person-years follow-up (events/follow-up in years)**		**Rate difference* per 10,000 person-years)**	**Matched hazard ratio (95% CI)**	***P* value**
	Placebo (n=1838)	**Eplerenone (n=1838)**			
Death from any cause	1430 (336/2350)	1058 (260/2457)	−372	0.71 (0.59–0.85)	<0.0001
CV hospitalization or CV death	3029 (603/1991)	2438 (518/2125)	−591	0.82 (0.72–0.94)	0.003
Secondary end points					
Death from CV causes	1255 (295/2350)	916 (225/2457)	−339	0.72 (0.59–0.87)	0.001
Sudden death from cardiac causes	511 (120/2350)	374 (92/2457)	−137	0.71 (0.53–0.96)	0.028
Death from AMI	213 (50/2350)	155 (38/2457)	−58	0.72 (0.47–1.13)	0.150
Death from HF	328 (77/2350)	240 (59/2457)	−88	0.70 (0.47–1.04)	0.076
Hospitalization for AMI	723 (161/2227)	588 (138/2348)	−135	0.84 (0.66–1.07)	0.157
Hospitalization for HF	1258 (268/2130)	1116 (251/2250)	−142	0.87 (0.72–1.05)	0.135
No history of hypertension					
Primary end points	Placebo (n=1176)	Eplerenone (n=1176)			
Death from any cause	1091 (169/1548)	1086 (167/1537)	−5	0.91 (0.72–1.15)	0.435
CV hospitalization or CV death	2188 (298/1362)	2019 (277/1372)	−169	0.91 (0.76–1.10)	0.331
Secondary end points					
Death from CV causes	950 (147/1548)	898 (138/1537)	−52	0.89 (0.69–1.15)	0.360
Sudden death from cardiac causes	394 (61/1548)	338 (52/1537)	−137	0.75 (0.49–1.13)	0.170
Death AMI	233 (36/1548)	202 (31/1537)	−31	0.85 (0.51–1.40)	0.523
Death from HF	258 (40/1548)	241 (37/1537)	−17	1.00 (0.60–1.66)	1.000
Hospitalization for AMI	578 (86/1489)	629 (92/1463)	+51	1.05 (0.77–1.45)	0.744
Hospitalization for HF	902 (130/1442)	681 (100/1468)	–221	0.73 (0.55–0.97)	0.028

AMI indicates acute myocardial infarction; CI, confidence interval; CV, cardiovascular; HF, heart failure.

TABLE 3

Adverse events in patients with a history of hypertension

Adverse events, n (%)	History of Hypertension			No History of Hypertension		
	Placebo (n = 1838)	Eplerenone (n = 1838)	*P* value	Placebo (n = 1176)	Eplerenone (n = 1176)	*P* value
Cardiovascular disorder*	947 (51.7)	891 (48.7)	0.080	555 (47.4)	562 (47.8)	0.869
Respiratory disorder	437 (23.8)	402 (22.0)	0.182	295 (25.2)	266 (22.6)	0.147
Cough	99 (5.4)	91 (5.0)	0.602	81 (6.9)	67 (5.7)	0.235
Dyspnea	158 (8.6)	132 (7.2)	0.126	125 (10.7)	87 (7.4)	0.006
Pneumonia	68 (3.7)	53 (2.9)	0.195	40 (3.4)	28 (2.4)	0.141
Metabolic or nutritional disorder	381 (20.8)	319 (17.4)	0.010	188 (16.1)	193 (16.4)	0.823
Hyperkalemia†	41 (2.2)	60 (3.3)	0.056	16 (1.4)	38 (3.2)	0.003
Hypoglycemia	22 (1.2)	12 (0.7)	0.120	8 (0.7)	5 (0.4)	0.422
Hypokalemia†	29 (1.6)	9 (0.5)	0.002	15 (1.3)	6 (0.5)	0.051
Hyperuricemia‡	70 (3.8)	57 (3.1)	0.278	31 (2.6)	21 (1.8)	0.163
Neoplasm	35 (1.9)	31 (1.7)	0.710	18 (1.5)	23 (2.0)	0.529
Urinary tract disorder	270 (14.7)	292 (16.0)	0.313	112 (9.6)	146 (12.4)	0.029
Disorder of skin or appendages	113 (6.2)	127 (6.9)	0.350	85 (7.3)	81 (6.9)	0.748
Musculoskeletal disorder	107 (5.8)	111 (6.1)	0.780	76 (6.5)	80 (6.8)	0.804
Nervous system disorder‡	220 (12.0)	263 (14.4)	0.036	187 (16.0)	180 (15.3)	0.691
Psychiatric disorder	145 (7.9)	139 (7.6)	0.757	100 (8.5)	97 (8.3)	0.823
Gastrointestinal disorder‡	327 (17.8)	363 (19.8)	0.128	195 (16.7)	243 (20.7)	0.013
Endocrine disorder	14 (0.8)	20 (1.1)	0.308	5 (0.4)	12 (1.0)	0.142
Disorder in men§						
Gynecomastia	9 (0.8)	5 (0.4)	0.299	3 (0.3)	5 (0.5)	0.726
Impotence	9 (0.8)	9 (0.7)	1.000	10 (1.1)	10 (1.1)	1.000
Disorder in women‖						
Breast pain	1 (0.2)	1 (0.2)	1.000	2 (0.8)	0 (0.0)	0.499
Serum potassium ≥6 mmol/L‡¶	77 (4.2)	108 (5.9)	0.019	37 (3.2)	53 (4.5)	0.106

Adverse events, n (%)	History of Hypertension			No History of Hypertension		
	Placebo (n = 1838)	Eplerenone (n = 1838)	*P* value	Placebo (n = 1176)	Eplerenone (n = 1176)	*P* value
Serum potassium <3.5 mmol/L[‡¶]	269 (14.7)	176 (9.6)	<0.001	116 (9.9)	73 (6.2)	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.

[‡] *P*<0.05 indicates significant difference between patients with and without Hx-HTN.

[§] Among patients with Hx-HTN, 1200 men were in the placebo group and 1208 men were in the eplerenone group. Among those without Hx-HTN, 925 men were in the placebo group and 931 men were in the eplerenone group.

[/] Among patients with Hx-HTN, 633 women were in the placebo group and 621 women were in the eplerenone group. Among patients without Hx-HTN, 245 women were in the placebo group and 244 women were in the eplerenone group.

[¶] Data are based on laboratory measurements. Data were available for 3622 patients with Hx-HTN (1833 patients, placebo group; 1829 patients, eplerenone group) and 2345 patients without Hx-HTN (1170 patients, placebo group; 1175 patients, eplerenone group).