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Effect of eplerenone on clinical stability of Japanese patients with acute heart failure

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Running title: Eplerenone and clinical stability in AHF

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Abstract

Background

In the EARLIER (Efficacy and Safety of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure) trial, eplerenone did not reduce heart failure (HF) hospitalizations or all-cause mortality in 300 patients admitted for acute HF (AHF). However, the trial might have been underpowered for these endpoints, and a comprehensive overview of the effect of eplerenone on diuretic doses and patients' clinical stability is warranted.

Methods

The EARLIER trial included Japanese patients hospitalized for AHF randomly assigned to eplerenone or placebo over 6 months. Cox proportional hazards and mixed-effects models were used for analyses.

Results

Three hundred patients were included (mean age, 67 ± 13 years; 73% males). The median furosemide equivalent dose was 40 (20–62) mg at randomization. Patients with higher furosemide-equivalent doses had more severe signs and symptoms of congestion and a higher risk of all-cause mortality or HF hospitalization during 6-month follow-up (adjusted-hazard ratio per 10 mg/day increase = 1.25, 95% confidence interval: 1.05–1.49). Eplerenone significantly decreased furosemide-equivalent diuretic doses and b-type natriuretic levels throughout the follow-up (overall-joint- $p < 0.05$ for both) and reduced E/e' and inferior vena cava diameter at 4 weeks (both $p < 0.05$). Additionally, eplerenone significantly reduced left ventricular (LV) end-diastolic diameter at 24 weeks ($p < 0.05$).

Conclusions

Eplerenone treatment improved the clinical stability particularly during short period following hospitalization for AHF, translated by lower diuretic doses, natriuretic peptide levels, indirect markers of filling pressure and venous congestion, and a smaller LV volume.

Keywords; eplerenone; congestion; heart failure; natriuretic peptide; echocardiogram

Introduction

Hospitalization for acute heart failure (AHF) increases a risk of re-hospitalization for worsening heart failure (HF) within the post-discharge period (1); however, HF re-hospitalizations may represent a small fraction of the whole patient journey (2).

Mineralocorticoid receptor antagonists (MRA) are a well-established therapy for chronic HF with a reduced ejection fraction (HFrEF) (3,4) and may be effective for a preserved ejection fraction (HFpEF) (5,6); still, few studies have assessed the efficacy of MRAs in AHF. In the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial (N=360), high-dose spironolactone (100 mg), compared with placebo with or without spironolactone 25 mg, did not reduce N-terminal pro-b-type natriuretic peptide (NT-proBNP) levels and improve signs and symptoms of congestion within 96h in patients admitted to the hospital for AHF (7). However, the short follow-up period (96h) and relatively slow onset of spironolactone action (>48h) may have contributed to the neutrality of ATHENA (8). However, MRAs with a shorter onset of action, such as eplerenone, may be more attractive for use in the AHF setting.

In the Efficacy and Safety of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER) trial, eplerenone showed a neutral impact on the prognosis of 300 Japanese patients hospitalized for AHF (9). However, the primary endpoint of EARLIER was defined as the composite endpoint of cardiovascular (CV) death or first hospitalization from CV diseases, mirroring the Eplerenone in Patients With Systolic Dysfunction After Myocardial Infarction (EPHESUS) trial (10), not focusing on HF-specific events. EARLIER, therefore, was underpowered to assess the effect of eplerenone vs. placebo on HF-specific events, all-cause mortality or HF hospitalization, with only 7 (4.7%) vs. 11 (7.3%) events

occurring during the 6-month follow-up. Despite the neutrality of the trial for this outcome, the benefits of eplerenone treatment may be captured by diuretic dose intensification, clinical measures of stability, biomarkers, and echocardiogram (11,12), which were recorded in most patients participating in EARLIER.

The main aim of this post-hoc analysis from the EARLIER trial was to explore the effect of eplerenone on patients' clinical status, key biomarkers, and echocardiographic measures among patients hospitalized for AHF.

Methods

Study population

The details of the EARLIER trial have been published previously (9,13). In brief, EARLIER was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the effect of eplerenone treatment on the clinical outcomes of 300 patients hospitalized for AHF in Japan. AHF was defined as the presence of one of the following signs or symptoms of congestion: pulmonary rales, radiographic pulmonary congestive signs, or a third heart sound. Patients enrolled in the study at any point from 3 to 14 days after HF hospitalization were randomly assigned to either the eplerenone or placebo group. For patients who previously received MRAs therapy and those who had planned coronary revascularization therapy during a hospital stay, a serum potassium concentration >5.0 mmol/L or an estimated glomerular filtration rate (eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration formula (14)) <30 mL/min/1.73 m² were excluded from the trial.

All patients provided written informed consent before enrollment in the study. This study complied with the Declaration of Helsinki, and the local institutional review board approved this study.

Outcomes

At randomization and all pre-specified subsequent visits (day 2, week 1 and 2, month 1, 2, 3, 4, 5, and 6), we standardized the doses of oral loop diuretics to furosemide equivalents as previously reported (15): bumetanide 1 mg, torsemide 20 mg, and azosemide 60 mg were considered equivalent to 40 mg intravenous or 80 mg oral furosemide, and any dose of a thiazide diuretic was considered equivalent to 20 mg oral furosemide. Out-of-hospital diuretic intensification (ODI) was defined as any increase in the furosemide equivalent doses post-discharge.

Echocardiogram was performed at each site by trained examiners. Diastolic function was assessed from the pattern of mitral inflow by pulsed-wave Doppler. Mitral annular early diastolic velocity (e') was assessed at the septal and lateral sites of the mitral annulus using tissue Doppler imaging. E/A ratio, e' mean and E/ e' mean ratio were calculated (16). Inferior vena cava (IVC) were obtained as recommended (17).

Statistical analysis

Categorical variables are presented as frequencies (percentages), and continuous variables as mean \pm standard deviation or median (25th and 75th percentiles), depending on the distribution. Patients were categorized by tertiles of baseline furosemide-equivalent daily oral doses (1st tertile: ≤ 20 mg/day, 2nd tertile: 21–40 mg/day, and 3rd tertile: >40 mg/day). Comparisons of patient characteristics across

furosemide-equivalent diuretic dose groups were performed using analysis of covariance and Kruskal-Wallis and χ^2 tests, as appropriate.

Cox regression models were used to study the associations between furosemide-equivalent diuretic doses (*i.e.*, baseline doses, average in-hospital and out-of-hospital doses) and outcomes, which were (1) a composite of all-cause mortality or HF hospitalization; (2) an extended composite of all-cause mortality, HF hospitalization, ODI, or elevated b-type natriuretic peptide (BNP), which was defined as >30% increase in BNP at any time-point after randomization. Age, gender, and body mass index (BMI) were covariates for adjustment.

Analysis of covariance was used for changes in echocardiographic variables and BNP values due to the eplerenone treatment. A linear regression model was fitted, including the treatment group and baseline variables. The eplerenone effect on furosemide-equivalent diuretic doses or BNP values throughout follow-up was assessed using a mixed effect model with furosemide-equivalent diuretic doses or BNP as dependent variable (measured at baseline, day 2, week 1 and 2, and month 1, 2, 3, 4, 5 and 6), treatment group allocation (eplerenone vs. placebo) as an independent fixed-effects variable, and age, gender, systolic blood pressure, heart rate, and eGFR as adjustment covariates; the random intercepts were set at the patient 'ID' level with an unstructured covariance matrix.

Statistical analyses were performed using R version 3.4.0 (R Development Core Team, Vienna, Austria). Statistical significance was defined as a two-sided p-value <0.05.

Results

A total of 300 patients were included; the mean age was 67 ± 13 years, and 73% were males. The mean BMI was 25 ± 5 kg/m², 60% had New York Heart Association (NYHA) III or IV, the mean LV ejection fraction (LVEF) was $30\pm 8\%$, and the median BNP was 376 pg/mL (25th and 75th centiles 185–624 pg/mL). At randomization, 126 (42.0%), 76 (25.3%), and 98 (32.7%) had furosemide-equivalent diuretic doses ≤ 20 mg/day, 21–40 mg/day, and >40 mg/day, respectively. *Table 1.*

Patients with higher furosemide-equivalent doses had more frequent signs and symptoms of congestion, greater inferior vena cava (IVC) diameters, worse health status, as supported by the Kansas City cardiomyopathy questionnaire (KCCQ) clinical summary score, and walked shorter distances in the 6-minute walking test (all $p < 0.05$). *Table 1.*

Overall, patients randomized to eplerenone received lower doses than placebo during 6-month follow up (median, 95% CI=37.5 mg/day, 24.9 to 48.8 in the eplerenone group vs. a placebo “dose” of 45.2 mg/day, 25.4 to 48.9; $P < 0.05$).

Associations of furosemide-equivalent diuretic dose with study outcomes

Higher average doses of in-hospital and out-of-hospital furosemide-equivalent diuretics were associated with a higher risk of all-cause mortality or HF hospitalization (adjusted-hazard ratio [HR], 95% confidence interval [CI] per 10mg/day increase for in-hospital doses=1.19, 1.01 to 1.41, $P=0.04$; adjusted-HR, 95%CI per 10mg/day for out-of-hospital=1.20, 1.03 to 1.40, $P=0.02$). *Supplemental Table 1.*

Eplerenone and furosemide-equivalent diuretic doses

The length of hospital stay was not significantly different between the eplerenone/placebo groups (median, 95% CI=17 days, 15 to 20 in the eplerenone

group vs. 18 days, 15 to 22 in the placebo group; $P=0.37$). Compared to placebo, patients randomized to receive eplerenone received lower furosemide-equivalent doses throughout the follow-up period. *Figure 1*. In patients randomized to eplerenone, there was a greater decline in average doses of in-hospital (mean difference, 95%CI= -7.39 mg/day, -14.06 to -0.71; $P=0.03$) and out-of-hospital furosemide-equivalent diuretics (mean difference, 95%CI= -9.33 mg/day, -16.94 to -1.72; $P=0.02$). *Table 2 and Supplemental Figure 1*.

Effects of eplerenone treatment on natriuretic peptide levels, echocardiographic variables, congestive signs, symptoms, and quality of life

Compared to placebo, eplerenone treatment significantly reduced BNP levels from baseline to week 4 by 17% ($p=0.03$). *Table 2 and Figure 2*. Eplerenone decreased E/e' (mean difference, 95%CI= -2.34, -4.36 to -0.33; $P=0.02$) and IVC diameter (mean difference, 95%CI= -1.21 mm, -2.31 to -0.12; $P=0.03$) from baseline to week 4. The LV end-diastolic diameter (LVDD) was reduced ($P=0.02$), and LVEF showed a tendency to increase ($P=0.06$) with eplerenone (vs. placebo) from baseline to week 24. *Table 2*.

No significant differences in NYHA class, KCCQ scores, or leg edema were observed between the eplerenone/placebo groups. *Supplemental Table 2*.

Eplerenone effect on the extended composite outcomes, including ODI

Eplerenone treatment did not reduce the extended outcomes by adding ODI and BNP increments to the composite of HF hospitalization or all-cause mortality (all P -values >0.10). *Table 3*.

Discussion

The present study shows that Japanese patients hospitalized for AHF and those taking higher diuretic doses had more severe congestion, worse health status, and a higher risk of clinical events. Eplerenone significantly reduced diuretic doses throughout the follow-up period and lowered LV filling pressures, IVC diameter, and natriuretic peptide levels. Furthermore, eplerenone significantly decreased a LV volume from baseline to 6 months. Together, these data support the initiation of eplerenone in AHF to improve clinical stability.

The clinical relevance of our findings is supported by the results of EPHEMUS, where among patients with acute myocardial infarction (AMI) complicated by HFrEF, those randomized to eplerenone required lower furosemide-equivalent diuretic doses throughout the follow-up period (12). However, in EPHEMUS, baseline diuretic doses were low (mean dose \approx 25 mg), and the timing when eplerenone significantly first reduced diuretic doses was relatively long follow-up period for AHF (\approx 90days). These results may be influenced by a unique characteristic of patients enrolled in EPHEMUS (*i.e.*, all patients presented an AMI), and less likely supported the initiation of MRAs therapy for acute decompensated HF(12,18). Therefore, our results suggest that eplerenone has the potential for an early diuretic effect, which was corroborated by less requirements of diuretic intensification and lower natriuretic peptide levels, compared with placebo. Although body weight changes at week 1 with eplerenone did not reach statistical significance, body weight was not plausible surrogate of symptom relief in patients with AHF (19). Importantly, as clinicians were not aware of the treatment assignment, our results likely support that patients improved their congestive signs and symptoms as clinical stability, which led the clinicians to reduce furosemide-equivalent diuretic doses.

In the current study, patients in the eplerenone group were not discharged earlier than those in the placebo group despite the presented clinical benefit from eplerenone. The degree of congestion may partly influence the length of hospital stay, however, to a greater extent, healthcare practice and socioeconomic factors may determine the length of hospital stay, particularly in Japan where hospital stay are usually long (20,21).

Studies on spironolactone in AHF did not show concordant benefits to those seen herein with eplerenone. In ATHENA-HF, spironolactone did not lower natriuretic peptides or alleviate congestion at 96h. The reasons for this lack of benefit in early decongestion are likely related to the fact that oral spironolactone has a slow onset of action, and the metabolic process may take up to 48h, whereas eplerenone has a rapid onset of action (<6h), which is more attractive for use in AHF (22,23).

The benefits of MRAs therapy in increasing LVEF are clinically important. In the present study, eplerenone significantly decreased the LVDD and tended to increase LVEF from baseline to week 24. These findings may be explained by the anti-adverse remodeling effects of MRAs therapy (24). In the (Heart “OMics” in AGEing) HOMAGE trial, spironolactone significantly improved LVEF and decreased levels of markers expressing myocardial fibrosis over 9 months in patients at risk of developing HF (25). Furthermore, in the (Anti-Remodeling Effect of Canrenone in Patients with Mild Chronic Heart Failure) AREA IN-CHF trial, enrolling patients with chronic HF and LVEF $\leq 45\%$ on optimized HF treatments, canrenone as MRAs therapy significantly increased LVEF during a 12-month period compared with placebo (26). Other studies also highlighted that MRAs therapy improved LVEF in patients with HFrEF (27,28). The improvement in cardiac function at week 24 may partly explain our observation that eplerenone stabilized patient clinical status and reduced the need for diuretics in the outpatient setting.

To add to the potential advantages of eplerenone initiation in AHF, a registry study showed that among patients hospitalized for AHF and eligible for MRA therapy, when MRA therapy was not initiated during the hospital stay, >75% were not prescribed MRAs within the next year (29). Thus, HF hospitalizations may provide a key opportunity to improve MRA initiation. Taken together, the present study is first study to show the clinical efficacy of early initiation of eplerenone in patients hospitalized for AHF by assessing different metrics of congestion. Although spironolactone showed inconclusive results in ATHENA (7), our results may encourage clinicians to initiate MRA therapy, particularly eplerenone, for AHF to alleviate congestion-reducing diuretic requirements, along with objective improvements in cardiac structure and function, stabilizing the clinical status along the patient journey.

Limitations

Our results should be interpreted in light of several limitations. This study is a post-hoc analysis of randomized controlled trial with moderate sample size and relatively low event rates in Japan. For AHF, relatively low furosemide-equivalent diuretic doses and long hospital stay were observed, which may be impacted by socioeconomic status, and healthcare practices in Japan (20,21,30). In addition, although rates of HF re-hospitalization may be a measure of clinical stability, EARLIER was underpowered to assess this outcome. Further data are required to rigorously evaluate the effect of eplerenone as a clinically stabilizing agent in patients hospitalized for AHF. Baseline guideline-directed medical therapies were well-balanced between eplerenone and placebo groups; however, changes in doses of other guideline-directed medical therapies (which might impact cardiac structure and function) were not available in the dataset. We lacked the reproducibility data of

echocardiogram; however, echocardiogram was performed by experienced practitioners in each institution. In addition, several key echocardiographic variables were lacking such as left atrial volume and pulmonary artery systolic pressure. The reasons for the diuretic dose changes were not captured in this study, which may have influenced the interpretation of the current results.

Conclusions

In Japanese patients hospitalized for AHF, eplerenone treatment improved the clinical stability particularly during short period following hospitalization for AHF, translated by lower diuretic doses, natriuretic peptide levels, indirect markers of filling pressure and venous congestion, and a smaller LV volume. These findings support the initiation of eplerenone treatment in patients hospitalized for AHF.

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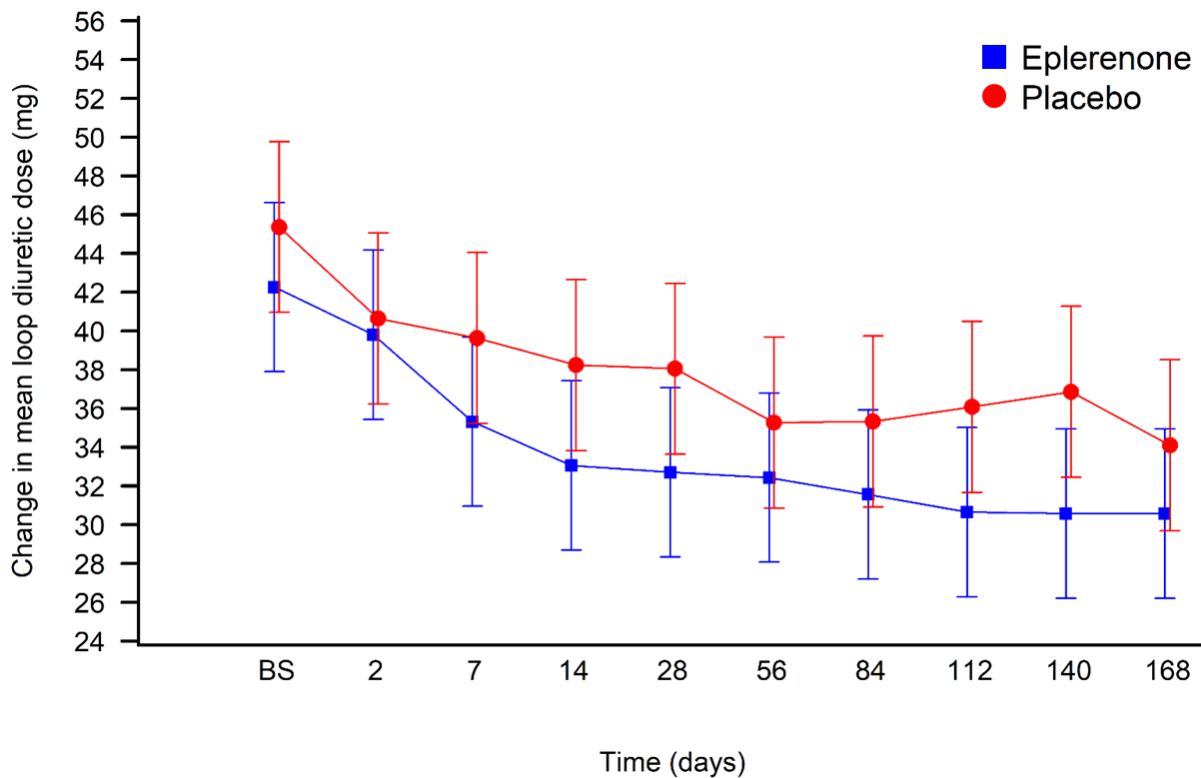
Figure 1. Effect of eplerenone/placebo on furosemide-equivalent diuretic doses over time

BS, baseline

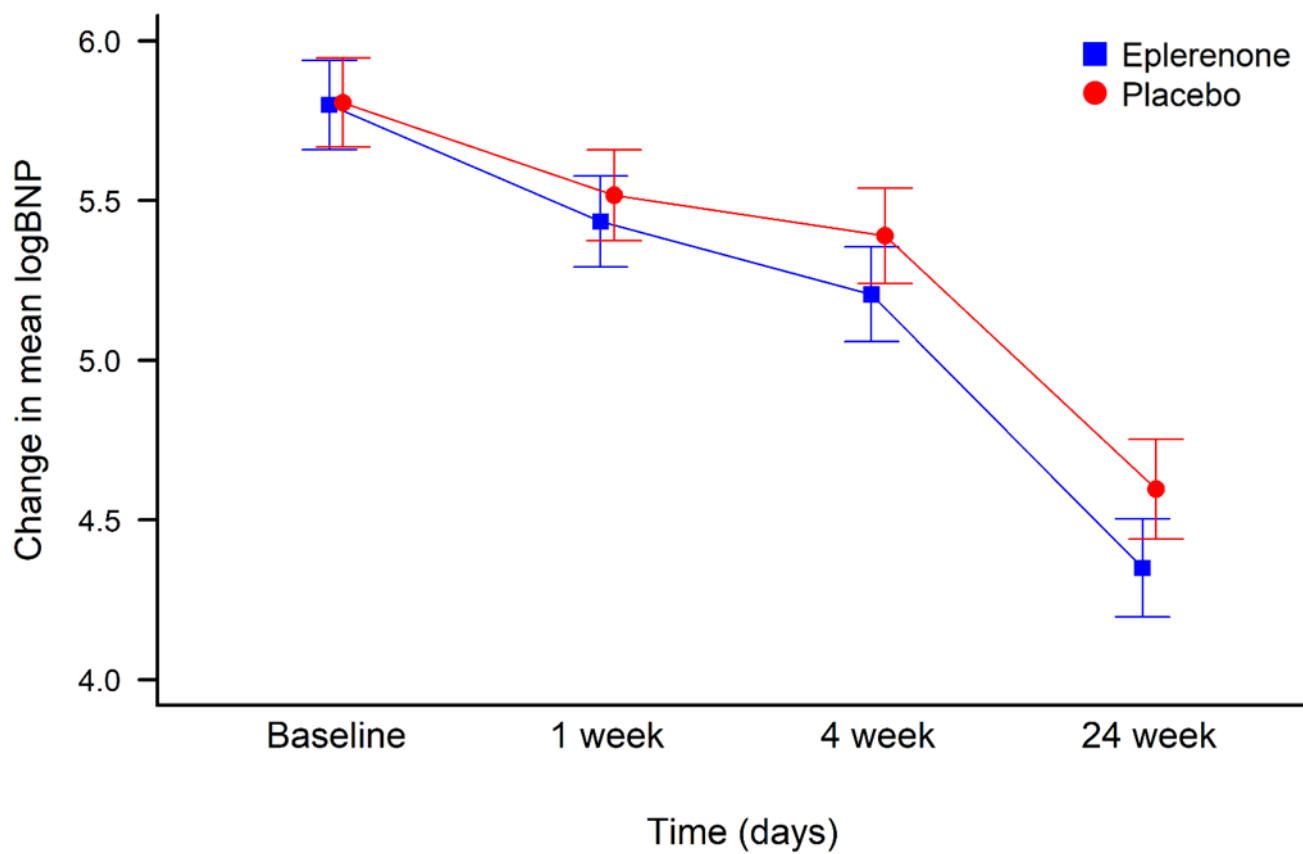
Figure 2. Effect of eplerenone/placebo on b-type natriuretic peptide over time

Log BNP, b-type natriuretic peptide transformed by natural logarithm

Figure 1. Effect of eplerenone/placebo on furosemide-equivalent diuretic doses over time



Overall joint $p = 0.03$

Figure 2. Effect of eplerenone/placebo on b-type natriuretic peptide over time

Overall joint $p = 0.02$

Table 1. Baseline characteristics according to the tertiles of furosemide-equivalent diuretic doses

Values are expressed as mean \pm SD, n (%) or median (25th to 75th percentile)

NYHA, New York Heart Association; AMI, acute myocardial infarction; HF, heart failure; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; JVD, jugular venous distention; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; IVC, inferior vena cava; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; KCCQ, Kansas city cardiomyopathy questionnaire.

Table 2. Eplerenone effect on doses of furosemide-equivalent diuretic, echocardiographic variables, and b-type natriuretic peptide

LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

*Analysis of covariance was used to assess the effect of eplerenone on changes in echocardiographic variables and b-type natriuretic peptide.

Table 3. Eplerenone effect on the extended composite outcome including out-of-hospital diuretic intensification, elevated b-type natriuretic peptide and the composite of all-cause mortality or heart failure hospitalization

HFH, heart failure hospitalization; ACD, all-cause mortality; ODI, out-of-hospital diuretic intensification; BNP, b-type natriuretic peptide.

*Out-of-hospital diuretic intensification was defined by any increments in the furosemide equivalent doses during the post-discharge period.

*Elevated BNP was defined as 30% increase in BNP at 1 month or more after randomization.

Table 1. Baseline characteristics according to the tertiles of furosemide-equivalent diuretic doses

	<20mg/day (N=126)	20-40mg/day (N=76)	>40mg/day (N=98)	p-value
Furosemide-equivalent diuretic dose at baseline, mg	10 (0 to 20)	40 (40 to 40)	80 (72 to 80)	<0.001
Age, years	67 (57 to 75)	68 (58 to 78)	68 (58 to 76)	0.87
Male, N (%)	100 (79.4%)	50 (65.8%)	68 (69.4%)	0.075
Body mass index, kg/m²	23.7 (21.2 to 26.5)	22.7 (20.4 to 26.1)	23.8 (21.0 to 27.6)	0.34
NYHA III or IV, N (%)	68 (54.0%)	46 (60.5%)	67 (68.4%)	0.09
Precipitated by AMI, N (%)	25 (19.8%)	5 (6.6%)	5 (5.1%)	<0.001
Ischemic etiology, N (%)	35 (33.7%)	20 (28.2%)	39 (41.5%)	0.19
Medical history, N (%)				
Hypertension	103 (81.7%)	55 (72.4%)	71 (72.4%)	0.17
Diabetes	47 (37.3%)	31 (40.8%)	42 (42.9%)	0.69
Dyslipidemia	78 (61.9%)	41 (53.9%)	52 (53.1%)	0.34
Myocardial infarction	23 (18.3%)	13 (17.1%)	22 (22.4%)	0.62
COPD	10 (7.9%)	3 (3.9%)	3 (3.1%)	0.23
Asthma	9 (7.1%)	6 (7.9%)	8 (8.2%)	0.96
Atrial fibrillation	40 (31.7%)	30 (39.5%)	35 (35.7%)	0.53
De novo HF	111 (88.1%)	69 (90.8%)	88 (89.8%)	0.82
Stroke or TIA	18 (14.3%)	15 (19.7%)	6 (6.1%)	0.03
Medications, N (%)				
ACEi or ARB	103 (81.7%)	55 (72.4%)	75 (76.5%)	0.28
Beta-blocker	81 (64.3%)	48 (63.2%)	63 (64.3%)	0.98
ACEi/ARB/Beta	69 (54.8%)	39 (51.3%)	48 (49.0%)	0.68
ACEi/ARB/BB/Eplerenone	36 (28.6%)	23 (30.3%)	17 (17.3%)	0.08
Aspirin	58 (46.0%)	28 (36.8%)	36 (36.7%)	0.27
Statin	59 (46.8%)	36 (47.4%)	38 (38.8%)	0.40
Systolic BP, mmHg	120 (108 to 137)	122 (107 to 140)	120 (103 to 132)	0.42
Heart rate, bpm	84 (73 to 97)	82 (73 to 99)	88 (74 to 101)	0.68
JVD, N (%)	43 (34.1%)	30 (39.5%)	40 (40.8%)	0.55
Rales, N (%)	66 (52.4%)	42 (55.3%)	68 (69.4%)	0.03
Leg edema, N (%)	50 (39.7%)	39 (51.3%)	53 (54.1%)	0.07
Hepatomegaly, N (%)	11 (8.7%)	7 (9.2%)	18 (18.4%)	0.06
Echocardiogram				
LVDD, mm	57 (53 to 64)	57 (52 to 63)	58 (52 to 63)	0.95
LVEF, %	31 (25 to 36)	31 (25 to 35)	30 (25 to 37)	0.99
E/A ratio	1.2 (0.8 to 1.8)	1.1 (0.7 to 1.4)	1.3 (0.8 to 2.3)	0.14
E/e' ratio	15.4 (11.6 to 20.1)	16.8 (12.1 to 21.5)	16.8 (11.3 to 21.8)	0.59
TRPG, mmHg	29 (22 to 41)	32 (26 to 40)	31 (24 to 40)	0.63
IVC, mm	17 (13 to 21)	18 (13 to 22)	20 (16 to 24)	0.02
Laboratory data				
Hemoglobin, g/dl	13 (12 to 15)	13 (12 to 15)	13 (12 to 15)	0.98
Sodium, mmol/l	141 (139 to 142)	141 (139 to 142)	141 (139 to 142)	0.81
Potassium, mmol/l	4.0 (3.8 to 4.3)	4.0 (3.8 to 4.3)	3.9 (3.6 to 4.1)	0.007
eGFR, ml/min/1.73m ²	63 (52 to 74)	60 (48 to 72)	61 (50 to 74)	0.29
BNP, pg/ml	337 (182 to 538)	386 (213 to 661)	445 (181 to 761)	0.11
Aldosterone	82 (53 to 128)	73 (54 to 112)	72 (45 to 106)	0.41
KCCQ score				
Overall summary	60 (35 to 80)	62 (38 to 77)	52 (32 to 70)	0.21
Clinical summary	69 (42 to 89)	67 (43 to 85)	57 (37 to 76)	0.025
6MWT at discharge, M	420 (336 to 500)	420 (335 to 482)	381 (280 to 460)	0.036
Eplerenone allocation	66 (52.4%)	38 (50.0%)	45 (45.9%)	0.63

Table 2. Eplerenone effect on doses of furosemide-equivalent diuretic, echocardiographic variables, and b-type natriuretic peptide

	Placebo (N=151)	Eplerenone (N=149)	Between-group changes	p-value
Loop diuretic doses				
Average in-hospital doses (mg/day)	35 (20 to 64)	31 (18 to 50)	-7.4 (-14.1 to -0.7)	0.03
Average out-of-hospital doses (mg/day)	40 (22 to 65)	27 (21 to 44)	-9.3 (-16.9 to -1.7)	0.02
Echocardiographic variables				
LVDD, mm				
Change from baseline to week 4	-0.9 (-3.3 to 2.6)	-1.9 (-4.0 to 1.0)	-0.9 (-2.3 to 0.4)	0.18
Change from baseline to week 24	-3.0 (-7.0 to 1.0)	-4.4 (-8.5 to -0.5)	-1.8 (-3.4 to -0.3)	0.02
LVEF, %				
Change from baseline to week 4	5.9 (1.0 to 14.2)	8.4 (2.0 to 16.0)	1.2 (-1.3 to 3.6)	0.35
Change from baseline to week 24	14.0 (7.0 to 22.0)	18.1 (9.0 to 27.0)	2.8 (-0.1 to 5.7)	0.06
E/e'				
Change from baseline to week 4	-1.9 (-8.4 to 1.8)	-3.8 (-7.9 to 1.3)	-2.3 (-4.4 to -0.3)	0.02
Change from baseline to week 24	-4.3 (-8.5 to 0.5)	-4.7 (-10.1 to -0.4)	-1.5 (-3.3 to 0.3)	0.11
Inferior vena cava, mm				
Change from baseline to week 4	-4.0 (-7.6 to 0.0)	-4.9 (-10.0 to 0.0)	-1.2 (-2.3 to -0.1)	0.03
Change from baseline to week 24	-4.9 (-11.0 to 0.0)	-4.0 (-10.1 to 0.5)	0.6 (-0.6 to 1.7)	0.34
Body weight, kg				
Change from baseline to week 1	-1.8 (-4.0 to -0.6)	-2.3 (-4.4 to -1.1)	-0.3 (-1.1 to 0.4)	0.35
Change from baseline to week 4	-1.9 (-5.1 to 0.5)	-2.5 (-5.0 to -0.7)	-0.7 (-1.7 to 0.3)	0.19
Change from baseline to week 24	-0.5 (-3.3 to 2.0)	-1.5 (-4.3 to 0.8)	-1.3 (-2.5 to -0.2)	0.03
eGFR, ml/min/1.73m²				
Change from baseline to week 1	-3.0 (-10.0 - 4.0)	-2.5 (-8.0 - 3.5)	-1.0 (-3.1 to 1.2)	0.37
Change from baseline to week 4	-1.0 (-9.0 - 8.0)	-2.0 (-10.0 - 6.0)	-1.5 (-4.4 to 1.4)	0.32
Change from baseline to week 24	-2.0 (-10.0 - 8.0)	-3.0 (-9.0 - 5.0)	-3.0 (-6.2 to 0.1)	0.06
BNP (pg/ml)				
Change from baseline to week 1	-57 (-258 to 42)	-108 (-315 to 16)	-65 (-122 to -9)	0.03
Change from baseline to week 4	-52 (-328 to 58)	-124 (-362 to 18)	-81 (-155 to -7)	0.03
Change from baseline to week 24	-205 (-471 to -48)	-213 (-495 to -49)	-14 (-57 to 29)	0.53

Table 3. Eplerenone effect on the extended composite outcome including out-of-hospital diuretic intensification, elevated b-type natriuretic peptide and the composite of all-cause mortality or heart failure hospitalization

	Placebo	Eplerenone	HR (95%CI)	z-score	p-value
	N (%) events	N (%) events			
HFH/ACM	7 (4.7%)	11 (7.3%)	0.55 (0.21 to 1.43)	-0.96	0.34
HFH/ACM/ODI	22 (14.6%)	20 (13.4%)	0.84 (0.38 to 1.87)	-0.43	0.67
HFH/ACM/BNP	57 (37.7%)	48 (31.8%)	0.83 (0.57 to 1.22)	-0.95	0.34
HFH/ACM/ODI/BNP	64 (42.4%)	56 (37.6%)	0.86 (0.60 to 1.23)	-0.85	0.39

Supplemental Table 1. Furosemide-equivalent diuretic doses (in mg/day) and study outcomes

	N (%) events	Diuretic	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
ACM and/or HF hospitalization	18 (6.0%)	Baseline (per 10mg)	1.06 (0.93 to 1.19)	0.38	1.08 (0.94 to 1.25)	0.26
		In-hospital* (per 10mg)	1.16 (0.98 to 1.37)	0.08	1.19 (1.01 to 1.41)	0.04
		Out-of-hospital* (per 10mg)	1.12 (0.99 to 1.27)	0.08	1.20 (1.03 to 1.40)	0.02

HR, hazard ratio; CI, confidential interval; ACM, all-cause mortality; HF, heart failure.

*indicates average furosemide-equivalent doses per days in in-hospital or out-of-hospital settings.

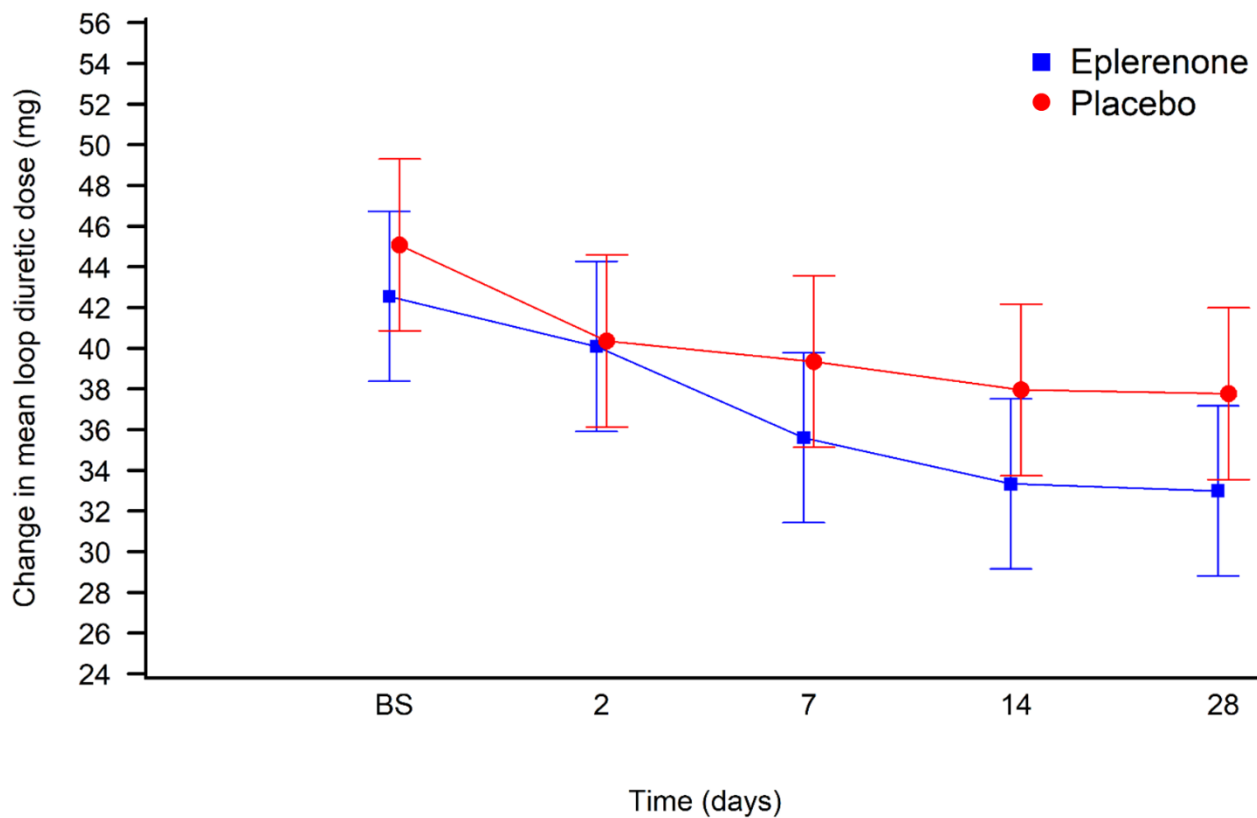
** adjusted for age, sex and body mass index.

Supplemental Table 2. Eplerenone effect on congestive signs, symptoms and quality of life

	Placebo (N=151)	Eplerenone (N=149)	Between-group-changes	p-value
New York Heart Association, N (%)				
Improvement from baseline to 1 week	104 (71.7%)	106 (73.6%)		0.72
Improvement from baseline to 4 weeks	109 (80.7%)	105 (80.2%)		0.90
No change or worsen from baseline to 1 week	41 (28.3%)	38 (26.4%)		0.72
No change or worsen from baseline to 4 weeks	26 (19.3%)	26 (19.8%)		0.90
KCCQ overall summary score				
Change from baseline to 4 weeks	18 (1 to 36)	22 (6 to 42)	3.37 (-1.00 to 7.73)	0.13
Change from baseline to 24 weeks	26 (11 to 49)	29 (10 to 48)	1.21 (-2.45 to 4.87)	0.52
KCCQ clinical summary score				
Change from baseline to 4 weeks	21 (5 to 40)	24 (7 to 45)	1.15 (-2.94 to 5.24)	0.58
Change from baseline to 24 weeks	24 (7 to 49)	29 (7 to 46)	-0.90 (-4.22 to 2.42)	0.60
Physical assessments, N (%)				
Jugular venous distention				
Improvement from baseline to 48 hours	45 (30.4%)	44 (29.9%)		0.93
Leg edema				
Improvement from baseline to 48 hours	47 (31.8%)	51 (34.7%)		0.59

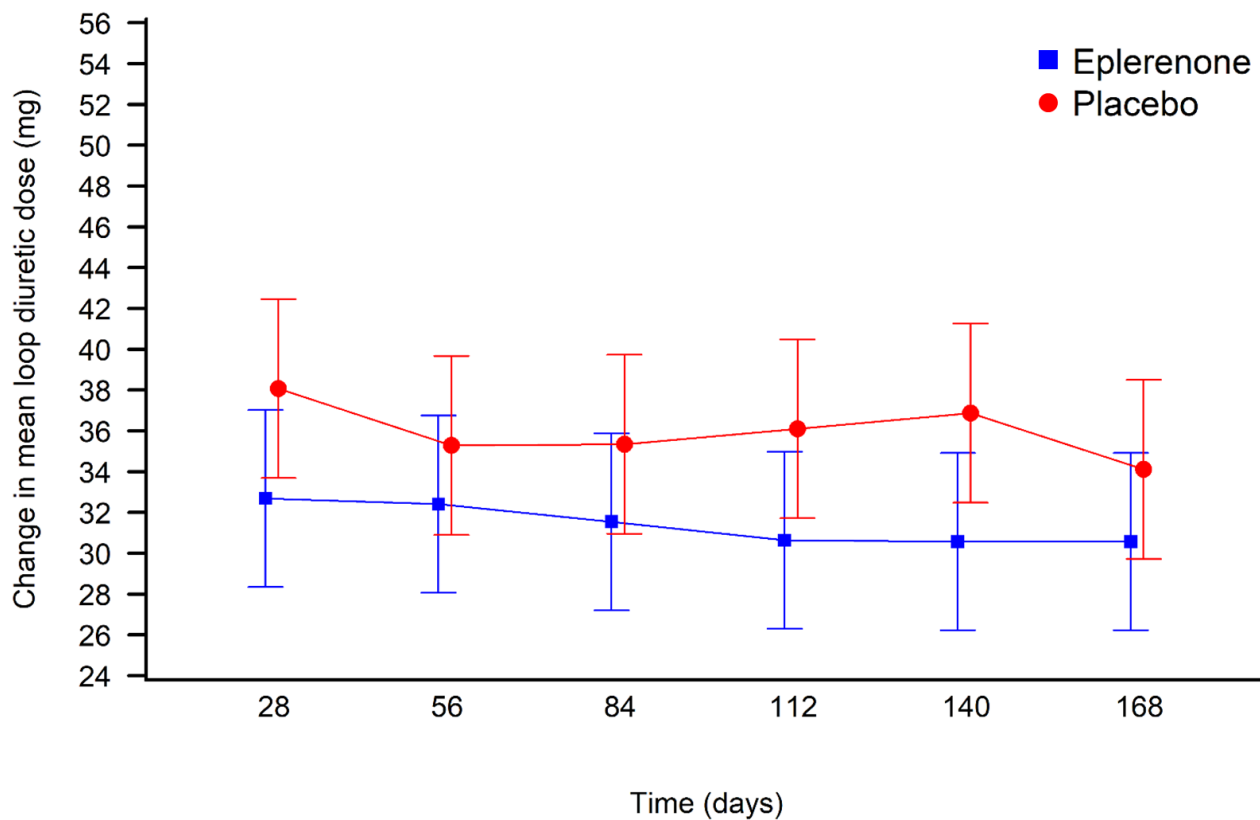
KCCQ, Kansas city cardiomyopathy questionnaire.

*Analysis of covariance was used for this analysis.

Supplemental Figure 1A. Effect of eplerenone/placebo on in-hospital doses of furosemide-equivalent diuretics

Overall joint $p = 0.04$

Supplemental Figure 1B. Effect of eplerenone/placebo on out-of-hospital doses of furosemide-equivalent diuretics



Overall joint $p = 0.03$