

Eplerenone Survival Benefits in Heart Failure Patients Post-Myocardial Infarction Are Independent From its Diuretic and Potassium-Sparing Effects

Insights From an EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) Substudy

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- Objectives** The purpose of this study was to determine whether a diuretic effect may be detectable in patients treated with eplerenone, a mineralocorticoid receptor antagonist, as compared with placebo during the first month of EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study) (n = 6,080) and whether this was associated with eplerenone's beneficial effects on cardiovascular outcomes.
- Background** The mechanism of the survival benefit of eplerenone in patients with heart failure post-myocardial infarction remains uncertain.
- Methods** A diuretic effect was indirectly estimated by changes at 1 month that was superior to the median changes in the placebo group in body weight (−0.05 kg) and in the estimated plasma volume reduction (+1.4%). A potassium-sparing effect was defined as a serum potassium increase greater than the median change in the placebo group: +0.11 mmol/l.
- Results** In the eplerenone group, body weight (p < 0.0001) and plasma volume (p = 0.047) decreased, whereas blood protein and serum potassium increased (both, p < 0.0001), as compared with the placebo group, suggesting a diuretic effect induced by eplerenone, associated with a potassium-sparing effect. A diuretic effect, as defined by an estimated plasma volume reduction, was independently associated with 11% to 19% better outcomes (lower all-cause death, cardiovascular death or cardiovascular hospitalization, all-cause death or hospitalization, hospitalization for heart failure). Potassium sparing was also independently associated with 12% to 34% better outcomes. There was no statistically significant interaction between the observed beneficial effects of eplerenone (9% to 17%) on cardiovascular outcomes and potassium-sparing or diuretic effects.
- Conclusions** Eplerenone's beneficial effects on long-term survival and cardiovascular outcomes are independent from early potassium-sparing or diuretic effects, suggesting that mineralocorticoid receptor antagonism provides cardiovascular protection beyond its diuretic and potassium-sparing properties. (J Am Coll Cardiol 2011;58:1958–66)
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Although recommended by current congestive heart failure (HF) management guidelines, long-term diuretic use is still a matter of controversy, since it may be associated with worse prognosis and is not supported by large-scale, randomized controlled studies. However, congestion is associated with worse outcome in patients with HF (1–3). The

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EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) study demonstrated that the addition of a low dose of the mineralocorticoid

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receptor blocker eplerenone to standard medical therapy (including diuretics) in patients with acute myocardial infarction and HF with left ventricular systolic dysfunction improved survival by 15%, with significant reductions in cardiovascular death, sudden death, and hospitalization for heart failure (4). In addition to a variety of pleiotropic effects (5), eplerenone may exert a diuretic, as well as a potassium (K)-sparing effect. The aim of the present study was to determine whether a diuretic and/or a K-sparing effect could be detected in patients treated with eplerenone in an EPHEUS substudy and, if any, whether these effects influenced cardiovascular outcomes.

Methods

Study design and patient population. The design and main results of the EPHEUS trial have been reported previously (4). The EPHEUS study enrolled patients with HF following acute myocardial infarction complicated by left ventricular systolic dysfunction (ejection fraction $\leq 40\%$). Heart failure had to be documented by at least 1 of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. Patients were entered into the study at any point from 3 to 14 days after the infarction. Patients with diabetes mellitus were not required to have evidence of HF. Among patients with biological assessment at month 1, 32% had diabetes (placebo vs. eplerenone: 32% vs. 32%). Only 4 diabetic patients (0.2%) had a left ventricular ejection fraction $>40\%$ at inclusion. The mean ejection

fraction was $32.6 \pm 6.2\%$ in diabetic patients versus $33.6 \pm 5.9\%$ in nondiabetic patients ($p < 0.0001$). All patients were randomly assigned to treatment with eplerenone 25 mg/day or placebo for the first month and up-titrated to 50 mg/day or placebo, depending on serum K levels. Treatment with eplerenone was in addition to standard medical therapy, which could include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, diuretics, aspirin, or statins, as well as coronary reperfusion therapy. EPHEUS was an event-driven study, and the mean duration of follow-up was 16 months.

Among the 6,632 patients enrolled in the EPHEUS study, 552 were excluded from the present analysis because of unavailable data at month 1 (259 [47%] died before 5 weeks, and 293 [53%] did not have the clinical and/or biological data requested for the diuretic-like effect assessment as defined later in the text). Therefore, 6,080 patients were included in our substudy (placebo: $n = 3,025$; eplerenone: $n = 3,055$) (Fig. 1), among which 5,692 were assessed at month 3 (placebo: $n = 2,837$; eplerenone: $n = 2,855$). Moreover, 351 patients were tested for brain natriuretic peptide (BNP) (Biosite, San Diego, California) at baseline and at month 1, as previously reported (6).

Estimation of the diuretic effect. A diuretic effect was defined post-hoc using 6 working definitions, with cutoffs taken as the medians observed in the placebo group:

1. Weight reduction >0.05 kg at 1 month
2. Estimated plasma volume reduction $>1.4\%$ at 1 month (plasma volume reduction was indirectly estimated using the Strauss formula (7,8):

$$\% \text{ change in plasma volume} = 100 \times \frac{\text{hemoglobin (before)}}{\text{hemoglobin (after)}} \times \frac{1 - \text{hematocrit (after)}}{1 - \text{hematocrit (before)}} - 100$$

We have also tested protidemia increase >4 g/l at 1 month as well as various combinations of any 2 of these tentative definitions, and we found these other definitions to be redundant (see the Results section). A K-sparing effect was defined as a change from baseline greater than the median change in the placebo group, that is, $>+0.11$ mmol/l. Dosage in furosemide equivalent doses (milligrams/day) for patients on loop diuretics were calculated as follows: 40-mg furosemide = 1-mg bumetanide = 10-mg piretanide = 10-mg torsemide (9).

Statistical analysis. All analyses were performed using SAS version 9.1.3 release (SAS Institute, Cary, North Carolina). The 2-tailed significance level was set to $p \leq 0.05$.

Continuous variables were described as mean \pm SD, and categorical data as frequency (percent). Comparisons of

Abbreviations and Acronyms

BNP = brain natriuretic peptide
eGFR = estimated glomerular filtration rate
HF = heart failure
MRA = mineralocorticoid receptor antagonist

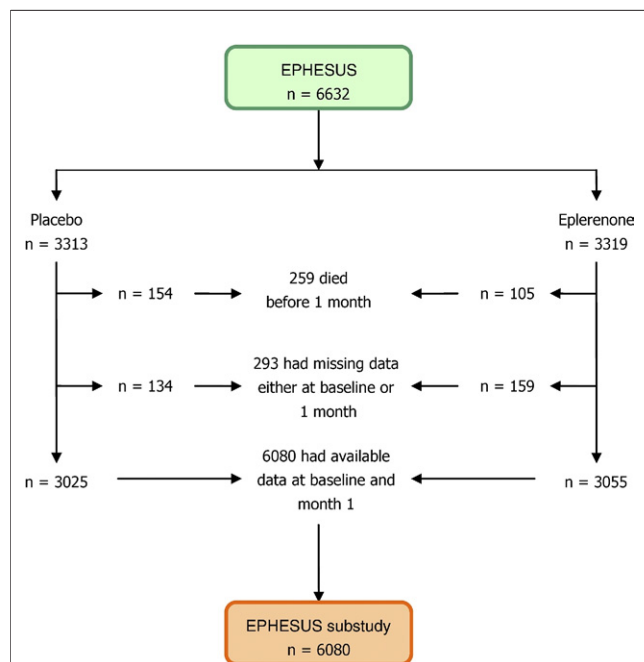


Figure 1. Flow Chart: Substudy Population

EPHEUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study.

treatment groups were carried out using the Mann-Whitney *U* test. Changes in the 2 treatment groups between baseline and 1 month on the one hand and between 1 and 3 months on the other hand were assessed using the group \times time interaction of repeated measures analysis of variance. These changes were graphically presented as unadjusted means at baseline, 1 month, and 3 months for patients with available data at baseline and 1 month for the first period, and at 1 and 3 months for the second. Correlation analyses into the subsample of patients with available biomarkers data were carried out using the Spearman correlation method. Association of crude rates of outcomes with quintiles of 1-month estimated plasma volume change from baseline was illustrated by plotting appropriate histograms; the trend analyses between quintiles and outcomes were performed using the Cochran-Armitage test. Because clinical signs of pulmonary congestion were not required in diabetic patients, interaction between diabetes and treatment group was additionally tested using the Breslow-Day test for *K* and plasma volume responses.

Time-to-event analyses, using 6 adjudicated outcomes— all-cause death (first primary endpoint), cardiovascular death or cardiovascular hospitalization (second primary endpoint), cardiovascular death, all-cause death or hospitalization, hospitalization for heart failure progression, or sudden death—were carried out in 1-month survivors, using the Cox proportional hazards model with an interactive backward selection method. Nine factors were tested as potentially associated with the outcomes: study drug, diuretic effect (see previous text), *K*-sparing effect, age at baseline, baseline *K*, baseline estimated glomerular filtration rate (eGFR) as assessed by the MDRD (Modification of Diet in Renal Disease) formula (10), eGFR change from baseline to 1 month, baseline mean blood pressure, and mean blood pressure change at 1 month. Study drug and diuretic effect were forced in all the models. All the validity assumptions of the Cox model were thoroughly checked (proportional hazards, log-linearity of the association between continuous covariables and risk, absence of interaction or collinearity). The covariables that did not meet the log-linearity assumption were dichotomized according to the median in the placebo group (estimated plasma volume and *K* change, see the previous text), or the shape of the curve when possible (mean blood pressure [MBP] and MBP change) or entered into the model as stratification factors otherwise. Additionally, estimated plasma volume and *K* changes were analyzed by quintiles in order to check that entering them as binary variables did not exclude some of their explanatory power and artificially inflated the estimated drug effect. Results were expressed as hazard ratios (95% confidence interval [CI]) and graphically presented as forest plots. Except for the main exposition factors (study drug, estimated plasma volume, and *K* effects), only significant covariables were retained in the final Cox models and displayed on graphic presentations.

Results

The main patient features in this EPHEBUS substudy are presented in Table 1. No significant difference was found between treatment groups. Compared with the remaining EPHEBUS population, the 552 patients excluded because of unavailable data at month 1 were generally older and sicker.

Eplerenone exerts early diuretic-like and *K*-sparing effects.

Body weight (placebo: 78 ± 15 kg vs. eplerenone: 79 ± 15 kg [$p = 0.38$]) and protidemia (placebo: 69 ± 7 g/l vs. eplerenone 68 ± 7 g/l [$p = 0.74$]) did not significantly differ at baseline between the study groups (Figs. 2A and 2C). After 1 month, we observed in both study groups a significant decrease in body weight (Fig. 2A) ($p < 0.0001$), an increase in plasma protein concentration (Fig. 2C) ($p < 0.0001$), and a decrease in estimated plasma volume (Fig. 2B) ($p < 0.0001$). These effects were of significantly higher magnitude in the eplerenone group (Figs. 2A to 2C), suggesting a diuretic-like effect of the study drug. This effect occurred early during the study, with the initiation dose of 25 mg once daily. Indeed, these differences were no longer significant between the first and the third month. Actually, despite the per-protocol up-titration to the higher dose of 50 mg once daily, plasma volume changes were of greater magnitude in the placebo group. Interestingly, over a 3-month period, neither the diuretic (besides eplerenone) intake (at inclusion: eplerenone [51%] vs. placebo [52%], $p = 0.60$; at month 1: eplerenone [52%] vs. placebo [53%], $p = 0.66$; at month 3: eplerenone [51%] vs. placebo [53%], $p = 0.12$) nor the furosemide-dose equivalent intake (for loop diuretics) differed significantly between both groups (at inclusion, median [extremes]: eplerenone: 40 [4 to 400] vs. placebo 40 [3 to 400] mg/day, $p = 0.69$; at month 1: eplerenone: 40 [4 to 400] vs. placebo 40 [3 to 300] mg/day, $p = 0.47$; at month 3: eplerenone 40 [4 to 375] vs. placebo 40 [3 to 240] mg/day, $p = 0.20$).

Using the kappa statistic to assess the relationship between the various definitions of a diuretic-like effect (based on weight decrease, protein increase, estimated plasma volume decrease, or various combinations of these parameters above the median in the placebo group), we observed that all of them were significantly correlated (kappa: $p < 0.01$) besides “weight decrease” and “estimated plasma volume decrease” (kappa: $p = 0.95$), which were selected to evaluate the association of the cardiovascular outcomes with the early diuretic effect. Indeed, the consistency between weight and plasma volume changes was found to be 50%, which means that there was as much chance of agreement as disagreement. The other definitions overlapped significantly (from 52% for weight/protidemia, to 66% for protidemia/plasma volume) and were not retained in the analyses since they had more chance of agreement than disagreement. Interestingly, in a subset of our study population tested for biomarkers, plasma volume changes between baseline and month 1 were significantly correlated with BNP concentration varia-

Table 1 Baseline Features of Patients With Available Data at Month 1 Versus Excluded Patients

	1-Month Survivors			
	Placebo (n = 3,025)	Eplerenone (n = 3,055)	All (n = 6,080)	Others (n = 552)
Age, yrs	64 ± 12	63 ± 11	64 ± 12	68 ± 11‡
Caucasians	2,747 (91%)	2,766 (91%)	5,513 (91%)	471 (85%)‡
Male	2,160 (71%)	2,186 (72%)	4,346 (71%)	368 (67%)*
Blood pressure, mm Hg				
Systolic	119 ± 16	119 ± 17	119 ± 16	118 ± 17†
Diastolic	72 ± 11	72 ± 11	72 ± 11	71 ± 12†
Left ventricular ejection fraction, %	33 ± 6	33 ± 6	33 ± 6	31 ± 7‡
Days from myocardial infarction to randomization	7 ± 3	7 ± 3	7 ± 3	8 ± 3
Previous hospitalization for heart failure	235 (8%)	222 (7%)	457 (8%)	55 (10%)*
Reperfusion therapy/revascularization	1,405 (46%)	1,405 (46%)	2,810 (46%)	196 (36%)‡
Symptoms of heart failure	2,532 (84%)	2,565 (84%)	5,097 (84%)	482 (88%)*
Serum potassium, mmol/l	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.2 ± 0.5†
Serum creatinine μmol/l	99 ± 28	100 ± 28	99 ± 28	107 ± 33‡
eGFR, ml/min/1.73 m ²	69 ± 19	68 ± 19	69 ± 19	63 ± 20‡
Medical history				
Acute myocardial infarction	794 (26%)	839 (27%)	1,633 (27%)	170 (31%)*
Diabetes	964 (32%)	972 (32%)	1,936 (32%)	206 (37%)‡
Heart failure	454 (15%)	430 (14%)	884 (15%)	91 (16%)
Hypertension	1,852 (61%)	1,823 (60%)	3,675 (60%)	332 (60%)
Medications				
ACEI/ARB	2,640 (87%)	2,639 (86%)	5,279 (87%)	472 (86%)
Beta-blockers	2,292 (76%)	2,305 (75%)	4,597 (76%)	364 (66%)‡
Diuretics	1,794 (59%)	1,800 (59%)	3,594 (59%)	390 (71%)‡
Aspirin	2,702 (89%)	2,691 (88%)	5,393 (89%)	477 (86%)
Statins	1,427 (47%)	1,421 (47%)	2,848 (47%)	247 (45%)
Digoxin	445 (15%)	424 (14%)	869 (14%)	135 (24%)‡
Amiodarone	240 (8%)	224 (7%)	464 (8%)	80 (14%)‡

Values are mean ± SD or n (%). No significant difference was found between treatment groups in 1-month available patients. *p < 0.05, †p < 0.01, ‡p < 0.001.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate.

tions ($r = 0.284$; $p < 0.0001$) independently from study drug and eGFR variations.

Baseline K levels did not differ significantly between patients assigned placebo or eplerenone (placebo: 4.3 ± 0.4 mmol/l vs. eplerenone 4.3 ± 0.4 mmol/l [$p = 0.15$]) (Fig. 2D). In both study groups, a significant increase in serum K concentration was observed after 1 month ($p < 0.0001$), and was of greater magnitude in the eplerenone group. This effect was more pronounced after 3 months in the eplerenone group (Fig. 2D). In parallel, K supplements were used more than twice as often in the placebo group, as compared with the eplerenone group after 3 months (9% vs. 4%, $p = 0.0006$).

Clinical signs of pulmonary congestion were not required at inclusion in diabetic patients, therefore interactions between diabetes and treatment group were additionally tested with regard to the plasma volume response and to the K response, and were not found significant (plasma volume response: $p = 0.50$; K response: $p = 0.56$).

Association of estimated early plasma volume depletion and the K-sparing effect with long-term cardiovascular outcomes. Independently from eplerenone use, and without any significant interaction, estimated plasma volume depletion, as defined in the preceding text, was consistently

significantly associated with a 11% to 19% improvement in most of the tested cardiovascular outcomes (all-cause death, cardiovascular death or cardiovascular hospitalization, all-cause death or cardiovascular hospitalization, and hospitalization for heart failure and a similar but nonsignificant trend [$p = 0.090$] for cardiovascular death), but not for sudden death (Fig. 3). Furthermore, across the spectrum of the tested cardiovascular outcomes (besides sudden death), the association between the intensity of the estimated plasma volume depletion and the crude event rates showed a significant linear trend in the whole study population (Fig. 4). In contrast, the weight-based definition of the diuretic effect was not significantly associated with any of the assessed outcomes (Fig. 3).

Independently from eplerenone use, and without any significant interaction, the K-sparing effect was associated with a significant 12% to 34% improvement of almost all tested outcomes, but not to all-cause death or hospitalization, nor to hospitalization for heart failure (Fig. 3). Similar significant or marginally significant trends were observed when analyzing the crude event rates (Table 2).

Multivariate analyses of the main cardiovascular outcome determinants confirmed that the eplerenone effect on car-

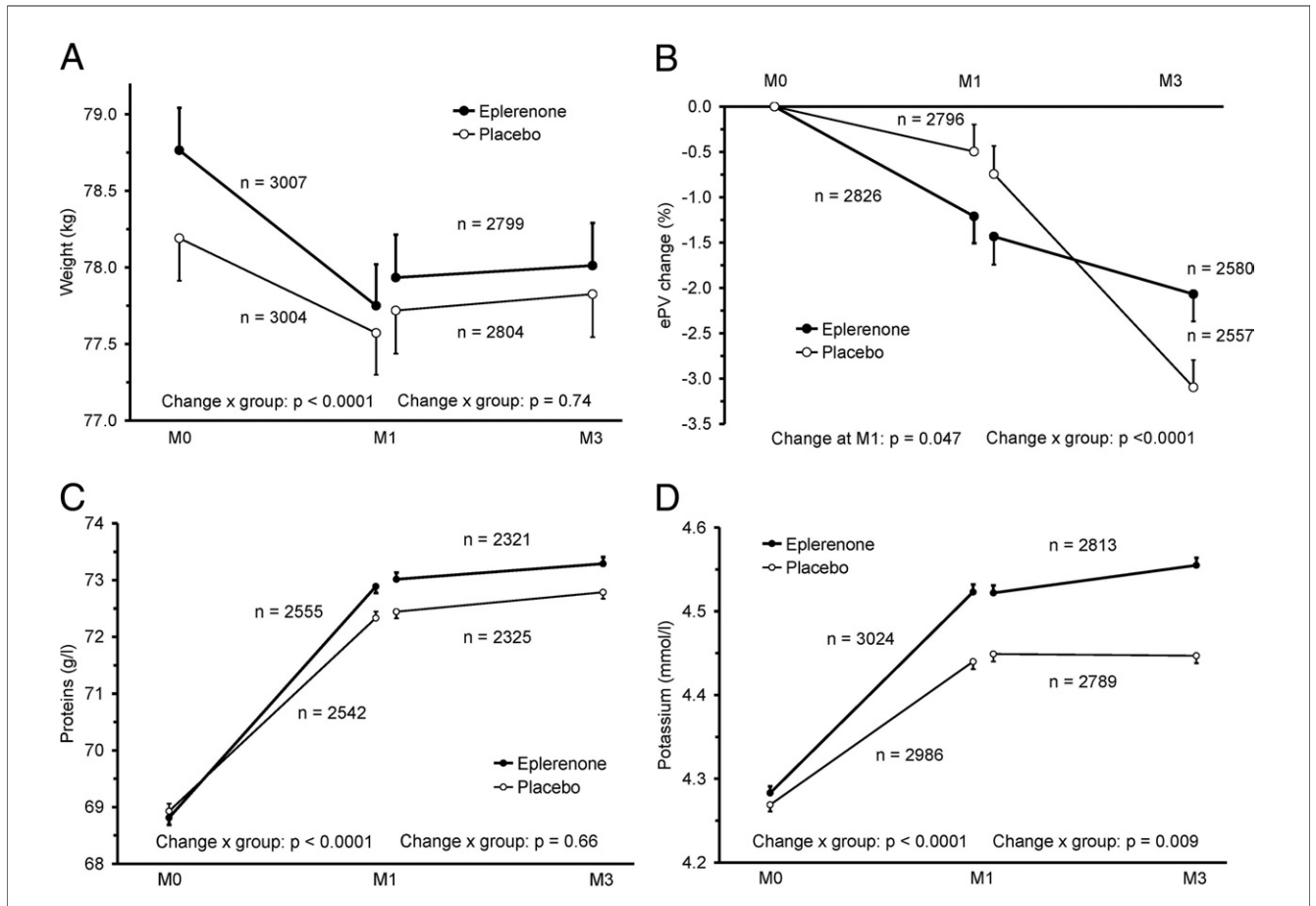


Figure 2 Eplerenone Exerts Early (1-Month) Diuretic-Like and K-Sparing Effects

Diuretic-like (A to C) and K-sparing (D) effects are shown. As a result of missing data, frequencies did not sum to 6,080 (M1) nor 5,692 (M3). M0-M1 and M1-M3 mean values are those for patients with available data at both ends of the period. Change at M1: single comparison of plasma volume change (Mann-Whitney test). Baseline values were set to zero for the graphical presentation. Change \times group: interaction between change from M1 to M3 and study group (repeated measures analysis of variance). ePV = estimated plasma volume; M0 = inclusion; M1 = month 1; M3 = month 3.

diovascular outcomes was independent from the early diuretic and K-sparing effects (analyzed as binary variables [Fig. 3]) or quintiles, data not shown), without any significant interaction. Indeed, eplerenone was associated with significantly better outcomes concerning cardiovascular death/hospitalization, all-cause death/hospitalization, and hospitalization for HF progression (Fig. 3), with nonstatistically significant positive trends concerning the other tested outcomes (all-cause death, cardiovascular death, sudden cardiac death).

Discussion

Our results show, for the first time to our knowledge, that in patients with HF and left ventricular systolic dysfunction complicating myocardial infarction, an initial and short-term diuretic-like effect, as defined by an estimated plasma volume decrease after 1 month, was associated with better cardiovascular outcomes. This occurred independently from a K-sparing effect, which was also associated with better outcomes. Although these diuretic-like and K-sparing ef-

fects were more pronounced with eplerenone, the benefit of eplerenone on outcomes was independent from the diuretic and K-sparing effects in the multivariate models. Thus, although our results suggest that a diuretic-like effect and a K-sparing effect of eplerenone can be detected in EPHEsus, the benefit of eplerenone on cardiovascular outcomes cannot be solely explained by these effects, suggesting additional protective cardiovascular pleiotropic effects of eplerenone.

Our results showing a beneficial effect of estimated plasma volume reduction are in accordance with growing evidence that hypervolemia by itself is independently associated with mortality in HF patients (1-3). More specifically, Androne et al. (11) showed that an increased blood volume, as assessed by intravenous administration of iodine-131-labeled albumin, was associated with an increased risk of death or urgent cardiac transplantation during a median follow-up of 719 days (1-year event-rate: 39% vs. 0%, $p < 0.01$). A meta-analysis of 3 small-sized ($N = 221$), short-term follow-up (4 to 52 weeks), randomized controlled trials of diuretic therapy in patients with HF showed a 65%

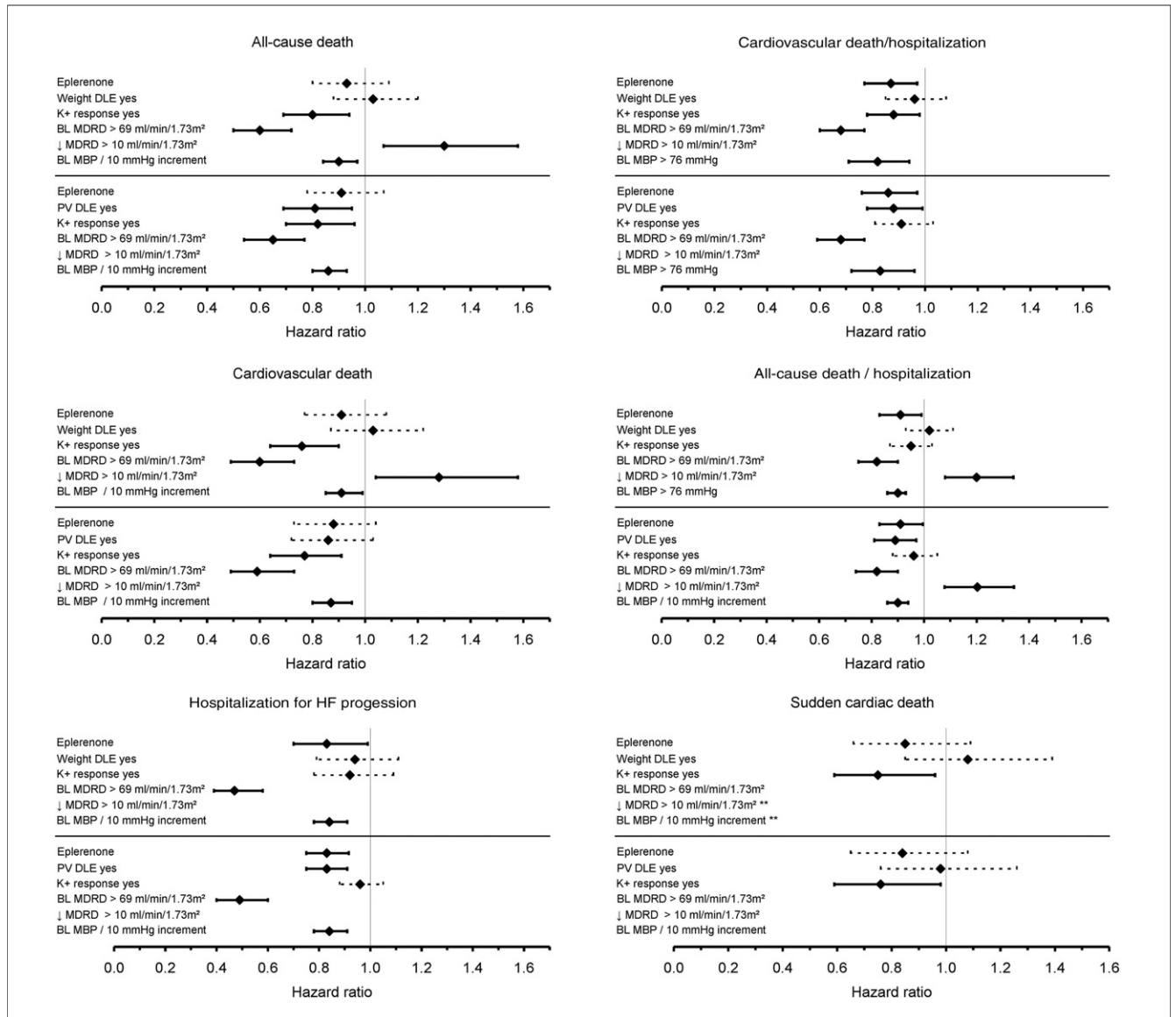


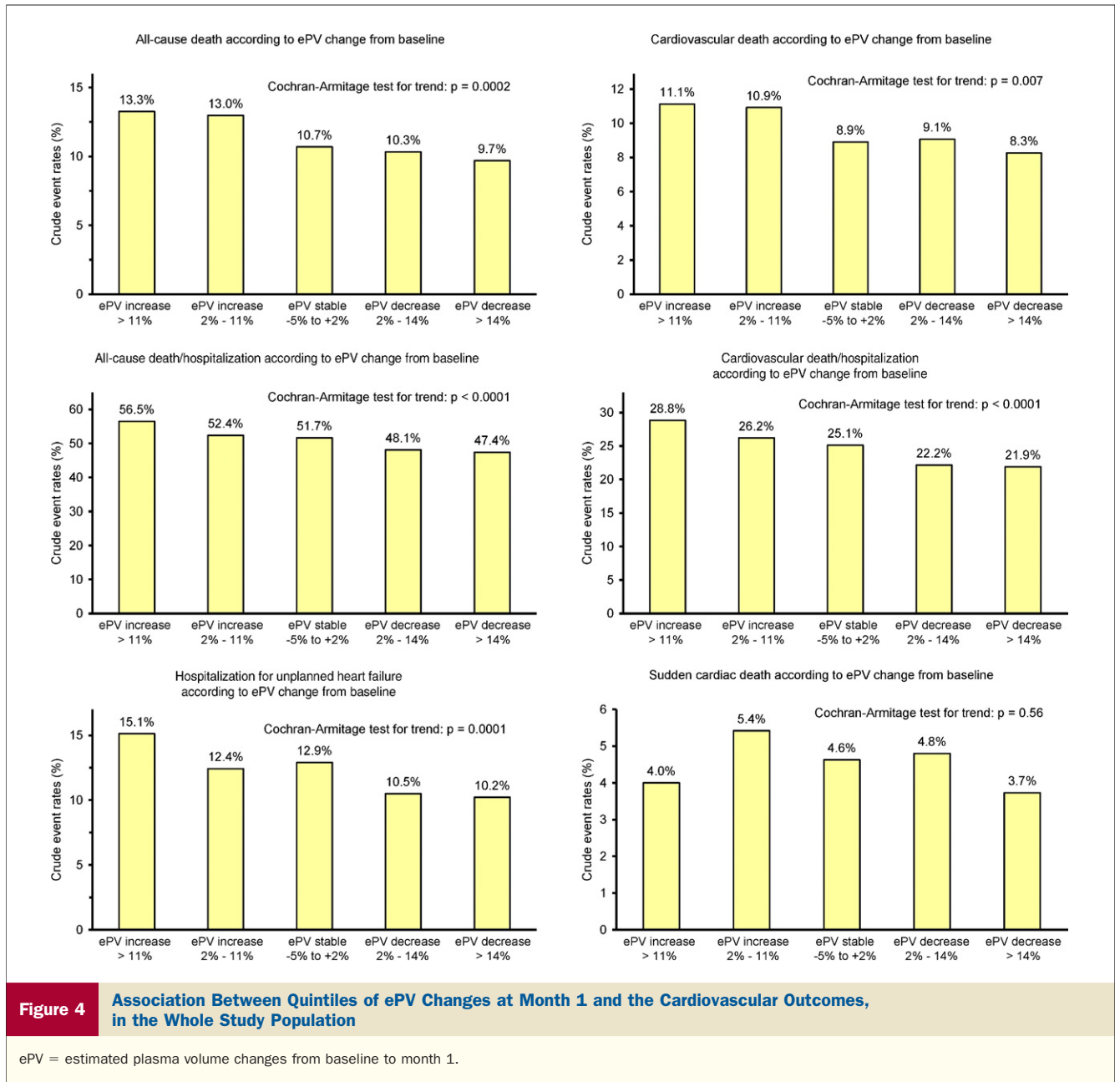
Figure 3 Determinants of the Cardiovascular Outcomes

Relationships of variables with outcomes are shown with the assessment of a diuretic effect either by body weight changes (upper half of each plot) or by estimated plasma volume changes (lower half of each plot) added into the model. Weight DLE indicates weight-based diuretic-like effect (included in the upper panels); ePV DLE indicates estimated plasma volume–based diuretic-like effect (included in the lower panels). Potassium response indicates the potassium-sparing effect; ↓ MDRD (Modification of Diet in Renal Disease) >10 ml/min/1.73 m² indicates a decrease between inclusion and month 1 in estimated glomerular filtration rate using the MDRD formula >10 ml/min/1.73 m². Covariables were removed from the models when they did not reach significance or have to be used as stratification factors in order to meet the models validity assumptions. BL = baseline; MBP = mean blood pressure.

reduction in mortality under diuretic therapy. If RALES (Randomized Aldactone Evaluation Study) (12) was also included, the overall odds ratio was 0.61 (95% CI: 0.50 to 0.74; $p = 0.0001$) (13). However, a variety of pathophysiological mechanisms suggest that diuretics may contribute to an increased mortality risk. Loop diuretics may activate the renin-angiotensin aldosterone and sympathetic nervous systems, and are associated with a decrease in the eGFR (14). Eshaghian *et al.* (14) reported in a survey of 1,354 consecutive patients with advanced systolic HF an independent dose-dependent association between loop diuretic use

and impaired survival. In post hoc analyses of the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) study (15) in 1,153 patients with advanced HF, as well as in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) trial (16,17), which enrolled 433 patients with severe chronic HF, high diuretic doses were independently associated with mortality.

That an early estimated plasma volume decrease, but not an extracellular and intracellular fluid volume depletion (i.e., weight decrease), was associated with better cardiovascular



outcomes, may suggest that short-term interventions that decrease volemia may provide long-term benefits on outcomes, in addition to symptoms. Our data therefore corroborate the hypothesis of Cotter et al. (18), which suggests that “in patients with predominantly acute cardiovascular failure, fluid overload, mostly in the form of pulmonary congestion, is caused by fluid redistribution rather than by fluid accumulation.” In this setting, studies examining the effect of vasodilators in patients with acute HF showed beneficial effects (18–20). Although a persistent increase in body weight after hospitalization for worsening HF is predictive of repeat hospitalization (21), weight loss in patients with acute HF may not be associated with improved symptoms or better outcome (18,22).

Potassium is an important determinant of myocardial function, and low serum K may cause arrhythmias and sudden cardiac death (23). Another major finding of the present study is that an early K-sparing effect, consistent with its mineralocorticoid receptor antagonistic effects, was significantly associated with improved long-term cardiovascular outcomes. Mineralocorticoid receptor antagonism (MRA) on top of standard medical care including angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) and beta-blockers has been adopted into both U.S. (24) and European (9) guidelines as a class I recommendation for the treatment of post-myocardial infarction HF. Many clinicians, however, are hesitant to use MRAs because of concerns about hyperkalemia as an

Table 2 Relationship Between the K-Sparing Effect and the Crude Event Rates

	Placebo K-Sparing Effect		Eplerenone K-Sparing Effect		p Value
	No	Yes	No	Yes	
All-cause death	12.8	11.6	11.9	10.4	0.083
All-cause death or hospitalization	53.7	52.0	49.2	50.5	0.86
CV death	11.2	9.7	10.3	8.4	0.018
CV death or hospitalization	26.7	26.5	25.6	22.4	0.084
Sudden cardiac death	5.3	4.7	5.1	3.5	0.061
Hospitalization for HF progression	13.4	13.1	12.2	11.0	0.63

The p values are treatment adjusted for association of K-sparing effect with outcomes.
CV = cardiovascular, HF = heart failure.

adverse effect. An EPHEBUS post-hoc analysis showed that the selective MRA eplerenone, when administered at a dose of 25 to 50 mg/day, is associated with a 4.4% absolute increase in the incidence of hyperkalemia (>5.5 mEq/l) and a 1.6% absolute increase in the incidence of more marked hyperkalemia (>6.0 mEq/l) that were not associated with outcomes at 30 days (p = 0.11) (25). The present data show that although an early rise in K was observed in the whole study population, it was more pronounced in patients receiving eplerenone (although K supplements were used more than twice as often in the placebo group) and was associated with better cardiovascular outcomes. In contrast, low serum K levels have been repeatedly shown to be associated with an increased risk of mortality due to all causes, cardiovascular causes, and progressive HF (23,26), whereas the use of non-K-sparing diuretics is associated with an increased risk of arrhythmic death (27).

Finally, we showed that even if eplerenone induced a diuretic effect, its use remained significantly associated with better cardiovascular outcomes independently from its K-sparing effects. Therefore, our data strongly support the hypothesis that a pleiotropic effect of the MRA eplerenone is involved in the pathophysiology of heart failure. These effects may involve left ventricular (6,28) and vascular (29) remodeling, including collagen synthesis, as well as effects on endothelial and immune function (5).

Study limitations. We performed a post-hoc analysis, including data-driven (median changes after 1 month in the placebo group) definitions of diuretic-like and K-sparing effects, since there is no consensual definition of these effects. The diuretic-like effect was assessed by a meaningful proposed (8) indirect estimation of plasma volume changes: a validated (upon comparison with a radio-labeled gold standard) method integrating hematocrit changes, which is routinely being used to estimate plasma volumes in patients scheduled plasma exchanges (30,31), or even ultrafiltration in the HF setting (32), whereas of note, no specific validation has been reported so far in the HF setting. However, sensitivity analyses performed in a subset of our study population showed significant positive correlations between BNP variations (presumably mainly triggered by variations in the level of congestion [33]) and plasma volume variations. Moreover, this formula also contains

hemoglobin ratios, and therefore controls for hemoglobin changes, which may matter in HF patients, within a cardiorenal anemia syndrome setting (34). We have elected to describe the diuretic and K-sparing effects at 1 month after randomization. Therefore, it is unknown whether these effects persist throughout long-term chronic drug exposure. Generally, long-term pharmacological effects of diuretics are difficult to characterize. In addition, considering values at later time points would have introduced a number of confounders and would have resulted in loss of observations due to event occurrence or dropout, and in loss of power and external validity. In addition, we have previously reported that the clinical benefit of eplerenone in EPHEBUS was already statistically significant at 1 month (35). Therefore, we believe that, although partially speculative, our findings and interpretations are acceptable. In any case, stemming from a post hoc analysis, they are mainly hypothesis generating and should be confirmed by further investigations. Importantly, our data are derived from a randomized controlled trial, thus allowing us to assess reliably the association between eplerenone use and the tested cardiovascular outcomes. However, even though we focused our analysis on the first month of follow-up, a minority of patients equally distributed between the 2 study groups (overall: 8.3%; eplerenone group: 7.9%, placebo group: 8.7%, p = 0.28) could not be included in the analysis because of unavailable data at month 1. In the meantime, within the EPHEBUS whole study population, the number of deaths was higher (153 of 3,313, 4.6%) in the placebo group, compared with the eplerenone group (107 of 3,319, 3.2%, p = 0.003). These already reported early beneficial effects on mortality (35) were not taken into account in our survival analyses, which used a starting point of 1 month post-enrollment. This may have contributed to the fact that the reported beneficial effects of eplerenone on all-cause death, cardiovascular death, and sudden cardiac death (4) were no longer found to be statistically significant in our substudy.

The external validity of these results concerning patients post-myocardial infarction with HF and altered ejection fraction remains to be assessed in other patient populations.

Conclusions

In the setting of HF post-myocardial infarction, our data provide important pathophysiological insights into eplerenone's beneficial effects which may involve but are independent from an early detectable significant diuretic and K-sparing effect.

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Key Words: clinical trial ■ diuretic ■ eplerenone ■ heart failure ■ potassium.