Impact of Eplerenone on cardiovascular outcomes in heart failure patients with hypokalemia

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Aims: Although hypokalemia is common among patients with heart failure (HF), the prognostic significance of baseline hypokalemia and hypokalemia during follow-up in HF patients receiving a mineralocorticoid receptor antagonist (MRA) remains uncertain.

Methods and results: Results of the EMPHASIS-HF trial in patients (n=2737) with HF and reduced ejection fraction with mild symptoms, randomized to Eplerenone or placebo, were analyzed with regard to the presence or occurrence of hypokalemia (serum K^+ <4.0 mmol/L) and the risk of cardiovascular death or hospitalization for HF (primary endpoint). Median follow-up was 21 months.

Baseline hypokalemia and hypokalemia during follow-up were common occurrences (19.6% and 40.6% respectively). Hypokalemia during follow-up was associated with worse outcomes in multivariable analyses (Hazard Ratio (HR) 1.26 (1.05-1.52), p=0.01) without evidence of interaction with Eplerenone. In contrast, baseline hypokalemia was associated with outcomes in the placebo group (HR 1.37, 1.05-1.79, p=0.02) but not in the Eplerenone group (HR 0.87, 0.62-1.23, p=0.44, p for interaction=0.04). Concurrently, Eplerenone was found to be more protective in patients with baseline hypokalemia vs. patients without baseline hypokalemia compared to placebo (HR 0.44 (0.30-0.64), p<0.001 vs. 0.69 (0.57-0.83), p=0.001; p for interaction=0.04). In patients without baseline hypokalemia, Eplerenone use decreased the rate of hypokalemia during follow-up (HR 0.69 (0.59-0.80), p<0.001). A potassium level above 4.0 mmol/L at one month after randomization mediated 26.0% (0.6-51.4%) of the Eplerenone treatment effect (p=0.04).

Conclusion: In HF patients receiving optimal therapy but not treated with Eplerenone, baseline hypokalemia was associated with worse outcomes. Conversely, hypokalemia amplified the treatment effect of Eplerenone.

Keywords: heart failure; potassium; prognosis

INTRODUCTION

Hypokalemia is common among patients with heart failure (HF), despite the use of inhibitors of the renin–angiotensin–aldosterone system (RAAS). In spite of this, the fear of inducing worsening renal function or hyperkalemia has hampered the initiation or increase in dosage of these lifesaving drugs in patients with HF and reduced left ventricular ejection fraction, who frequently have chronic kidney disease[1, 2]. Previous analyses in patients with HF noted poorer outcomes in those with potassium levels below 4.0 mmol/L defining hypokalemia, while incident hypokalemia was shown to be attenuated by the use of mineralocorticoid receptor antagonists (MRAs) in patients with NYHA stage III-IV enrolled in RALES (Randomized ALdactone Evaluation Study)[3-6]. We previously reported that, in patients after myocardial infarction with left ventricular dysfunction enrolled in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), an early rise in potassium levels at one month with the MRA Eplerenone was associated with better cardiovascular outcomes[7]. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) investigated the effects of Eplerenone, added to evidence-based therapy including RAAS inhibitors and beta-blockers on clinical outcomes, in patients with systolic HF and mild symptoms (i.e. NYHA functional class II symptoms). Eplerenone reduced the primary endpoint of cardiovascular death or HF hospitalization in comparison with placebo when added to evidence-based therapy. Although the use of Eplerenone was associated with a higher incidence of worsening renal function and hyperkalemia, it retained its survival benefits without any significant interaction with the association between hyperkalemia (>5.5 mmol/L) and worsening renal function and worse outcomes[8]. While hypokalemia was reported by investigators as an adverse event, hypokalemia tended to be less

common in the Eplerenone group than in the placebo group (1.2% vs. 2.2%, p=0.05)[9]. Eplerenone furthermore induced a significant, early and persistent, albeit modest, rise in serum potassium (of approximately 0.1 mmol/L after one week)[8]. Because of protocol-mandated serial monitoring of serum potassium, we were also able to analyze actual changes in potassium, as opposed to merely investigator-reported events. In the present study, we assessed the prevalence, incidence, associated factors, and prognostic significance of hypokalemia at baseline or occurring during follow-up in patients enrolled in EMPHASIS-HF. We also assessed the interaction between prevalent hypokalemia and hypokalemia during follow-up and the effect of Eplerenone on clinical outcomes.

METHODS

Study Design and Patient Population

The design and main results of the EMPHASIS-HF trial have previously been reported[10]. Of note, patients with a serum potassium >5.0 mmol/L, or an estimated glomerular filtration rate (eGFR)[11] <30 ml/min/1.73 m^2 within 24 hours prior to randomization or requiring a potassium-sparing diuretic were not included. The study was approved by an institutional review committee and the subjects gave informed consent (ClinicalTrials.gov number, NCT00232180). A *post-hoc* analysis was performed in all 2737 patients included in the EMPHASIS-HF trial. Median follow-up was 21 months. Per-protocol dosing requirements based on serum potassium were performed according to a therapeutic algorithm as previously reported[8]. Briefly, serum potassium concentration was measured at four weeks and each subsequent clinic visit (every 4 months (Months 5, 9, 13, 17, 21, 25, 29, 33 and 37), then after 5 months (Month 42) and then after 6 months (Month 48) and subsequently at six-month

intervals until early termination or initiation into the open label phase), with the dosage of study drug (Placebo/Eplerenone) adjusted according to the algorithm. Additionally, the concentration of serum potassium was verified one week after any dose adjustment.

Endpoints

The primary efficacy endpoint for the EMPHASIS-HF trial was the composite of cardiovascular mortality or hospitalization for HF. Hospitalization for HF and cardiovascular mortality were secondary endpoints. All endpoints were independently adjudicated by an independent Critical Event Committee and were used for this post-hoc analysis.

Statistical analysis

"Hypokalemia" was defined as a serum potassium < 4.0 mmol/L and "mild hypokalemia" as 3.5 d serum K^+ < 4 mmol/L for sensitivity analysis[3].

Between-group assessments of baseline characteristics were performed using t-tests for continuous variables and Fisher's exact tests for categorical variables.

The association between baseline characteristics and the presence of baseline hypokalemia was assessed using logistic regression models. The following baseline covariates were chosen *a priori*, based on a pathophysiological standpoint: study treatment, age, gender, ethnicity (White vs. others), body mass index (BMI), systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin, ejection fraction, diabetes, history of myocardial infarction, history of

hospitalization for heart failure, estimated glomerular filtration rate (eGFR), use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB), % of ACE-I or ARB target dose, use of beta blockers, % of beta blocker target dose, use of loop diuretics, daily dose of loop diuretics use (furosemide equivalents), use of other diuretics, use of digitalis, and intake of potassium supplements. Analysis was performed either including all covariates in the model (for the models presented in Table 2) or, for other models, using stepwise selection to retain only those covariates shown to be significantly associated with baseline hypokalemia in the multivariable model ($p<0.05$).

Cox proportional hazard regression models were used to examine the associations between the above covariates and the following endpoints:

- cardiovascular death or heart failure hospitalization (primary endpoint)
- cardiovascular death
- occurrence of hypokalemia post-baseline

For the Cox regression analyses, patients who did not have an endpoint event were censored at the date of death (non-CV death for the primary endpoint or the endpoint of cardiovascular death), date of withdrawal, or study cut-off date (May 25 2010), whichever occurred first.

The interaction of treatment and baseline hypokalemia or hypokalemia during follow-up on the rate of the primary endpoint and on the rate of post-baseline hypokalemia was examined using Cox proportional hazard models similar to those described above.

The interaction of treatment and hypokalemia during follow-up on the rates of primary endpoint was also examined using Cox proportional hazard models similar to those described above. However, for this analysis, hypokalemia during follow-up was treated as a time-(varying, factor, i.e. the model used an indicator variable for this factor that assumed the value of 0 until the first occurrence of hypokalemia and the value of 1 thereafter. As a sensitivity analysis, similar Cox proportional hazard analyses were also performed using the incidence of hypokalemia at Month 5 as the incident hypokalemia factor. For patients with events occurring prior to Month 5, the last available post-baseline potassium measurement prior to the event was used (last observation carried forward method).

All aforementioned baseline covariates chosen *a priori*, based on a pathophysiological standpoint, were included as adjustment variables in the multivariable Cox models.

Kaplan-Meier curves were generated to illustrate the risk of endpoints in various participant subsets.

In a sensitivity analysis, the time to first hypokalemia was estimated by first using the midpoint between the visit at which hypokalemia was observed and the previous visit and second visit using linear interpolation to estimate the time at which the potassium level fell below 4.0. The results using either method were similar (data not shown) to the original analysis. As our results were consistent regardless of the method used, including the simplest method (no interpolation), the latter was ultimately retained throughout the present analysis.

To determine the portion of the Eplerenone treatment effect attributable to the early[7] increase in potassium level above the level defining hypokalemia (as defined by a Month 1 level of 4.0 mmol/L or greater), mediation analyses were performed using the %MEDIATE macro developed by Hertzmark et al[12] based on the methods of Lin et al[13].

The macro, applied in patients with baseline hypokalemia, compared a model (Model 1) that included treatment as a factor (the exposure) and an indicator for the increase in potassium level to 4.0 or greater (the intermediate variable) with a model (Model 2) that eliminated the intermediate variable. From the coefficient estimates, the proportion mediated by the intermediate variable was calculated by the following formula:

(1 - (estimate for treatment in model 2 / estimate for treatment in model 1) * 100

The standard error of the above estimate was calculated in the manner of Lin et al[13], using the values of the coefficient estimates as well as the associated covariance matrix. A 95% confidence interval was obtained by first using Fisher's z transformation and the delta method to obtain the 95% confidence limits of the transformed estimate, followed by back-transforming to report the 95% confidence interval on the original scale. A similar analysis was performed to determine the portion of the Eplerenone treatment effect attributable to the increase in potassium level above the level defining hypokalemia at Month 5. For patients with events occurring prior to Month 5, the last available post-baseline potassium measurement prior to the event was used.

In the present analysis, odds ratios and hazard ratios are presented with the associated 95% confidence interval and p-value. For summaries of categorical variables, count/total

population and percentage are presented. For summaries of continuous variables, mean ± standard deviation (SD) is presented.

A p-value of <0.05 was considered statistically significant for all analyses except the analyses of interactions. Given the low power of interaction tests [14-16], we, [17] as others [16, 18-20], selected a priori a 0.10 cut-off threshold for interaction p-values.

All analyses were conducted by Pfizer and inVentiv Health Clinical with the original trial dataset using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Prevalence and factors associated with baseline hypokalemia

Patient characteristics according to the presence or absence of baseline hypokalemia and treatment allocation are described in table 1 (and eTable for mild baseline hypokalemia). Overall, baseline hypokalemia was a common occurrence (N=536/2737, 20%), was mostly mild (468/536 = 87%) and equally distributed in both the Eplerenone and placebo groups. Of note, approximately 10% of study participants across all subgroups were receiving potassium supplements (Table 1 and eTable).

In multivariable analysis, higher ejection fraction (OR 0.98 (0.95-1.00), p=0.024), white ethnicity (OR 0.45 (0.35-0.58), p<0.001) and history of diabetes (OR 0.78 (0.62-0.97), p=0.029) were associated with a lower risk of baseline hypokalemia. In contrast, higher eGFR (OR 1.06 per 10-unit increase (1.01-1.11), p=0.014), loop diuretics use (OR 1.39 (1.07-1.80), p= 0.014) and other non-potassium sparing diuretics use (1.83, 1.43-2.34, p<0.001) were significantly associated with a higher risk of baseline hypokalemia.

Prognostic value of baseline hypokalemia and interaction with Eplerenone

Survival curves in patients with and without baseline hypokalemia are provided in figure 1.

Overall, in multivariable analysis, baseline hypokalemia was not significantly associated with increased rates of the primary outcome (HR 1.14 (0.93-1.41), p= 0.22) and cardiovascular death (Table 2).

Using a multivariable Cox model, a significant interaction was identified between baseline hypokalemia and Eplerenone for the primary outcome (interaction p value: 0.04).

Importantly, baseline hypokalemia was significantly associated with poorer outcome in the placebo group (HR 1.37 (1.05-1.79), p=0.02) as opposed to no association with outcome in the Eplerenone group (Table 2). In addition, the magnitude of treatment effect of Eplerenone was greater in patients with baseline hypokalemia (HR 0.44 (0.30-0.64), p<0.001) (Figure 1 and Table 2), a finding also confirmed in a sensitivity analysis encompassing patients with mild baseline hypokalemia (HR 0.44 (0.29-0.65), p<0.001).

Incidence and factors associated with hypokalemia during follow-up

Overall, hypokalemia during follow-up prior to the primary outcome was common (40.6%), although far more frequent in the placebo group than in the Eplerenone group (618/(618+755) or 45%, vs. 494/(494+870), or 36%, p<0.001). When considering all hypokalemia during follow-up (i.e. including those occurring after HF hospitalization), the same pattern was observed (overall 42.6%, 648/648+725 or 47% in the placebo group vs. 519/519+845 or 38% in the Eplerenone group).

Univariable analysis of baseline features of patients experiencing hypokalemia during follow-up are depicted in Table 1. In multivariable analysis (Table 3), Eplerenone use was associated with a decreased rate of hypokalemia during follow-up, while hypokalemia at baseline was strongly associated with a higher rate of hypokalemia during follow-up (HR 3.04 (2.66-3.47), p<0.001). There was no significant interaction between baseline hypokalemia and Eplerenone with regard to the rate of hypokalemia during follow-up (p value for interaction= 0.40), suggesting that Eplerenone had a similar effect on rates of hypokalemia during follow-up in patients with and without hypokalemia at baseline. When focusing on patients without hypokalemia at baseline, higher eGFR, loop diuretics, other diuretics and potassium

supplements were significantly associated with higher rates of hypokalemia during follow-up whereas Eplerenone was associated with decreased rates of hypokalemia during follow-up (Table 3). Of note, patients with chronic kidney disease (CKD as defined by a baseline eGFR <60 ml/min/1.73 m^2) did not significantly differ from those without CKD, regardless of the treatment group considered in terms of hypokalemia occurrence (e-figure).

Prognostic significance of hypokalemia during follow-up and its interaction with Eplerenone treatment

In multivariable analysis, there was no significant interaction between hypokalemia during follow-up and Eplerenone with regard to the primary outcome (interaction p value = 0.44) or cardiovascular mortality (interaction p value = 0.79). Similarly there was no interaction between hypokalemia at Month 5 and Eplerenone (p for interaction = 0.73).

Hypokalemia during follow-up (coded as a time-dependent variable) and hypokalemia at 5 months were both significantly associated with higher rates of the primary outcome and of CV death (Table 2).

Mediation sensitivity analysis

In the subset of patients with baseline hypokalemia, a significantly greater percentage of patients in the Eplerenone group exhibited a serum K^+ e 4.0 mmol/L at Month 1 than in the placebo group: 186/268 (69.4%) versus 138/268 (51.5%), p<0.001. For most demographics and baseline characteristics, no difference was observed between patients with serum K^+ e 4.0 mmol/L and those with serum K^+ < 4.0 mmol/L at Month 1 (data not shown).

However, a greater percentage of patients with serum K^+ e 4.0 mmol/L at Month 1 were white as opposed to those with serum K^+ < 4.0 mmol/L at Month 1, both in the Eplerenone [139/186 (74.7%) versus 50/82 (61.0%), p=0.03] and placebo [111/138 (80.4%) versus 88/130 (67.7%), p=0.02] groups. In addition, in the Eplerenone group, a lower percentage of patients with a serum K^+ e 4.0 mmol/L at Month 1 were receiving loop diuretics [142/186 (76.3%) versus 72/82 (87.8%), p=0.03].

Mediation analysis showed that the increase in serum potassium above 4.0 mmol/L at one month after randomization mediated 26.0% (0.6 to 51.4%) of the Eplerenone treatment effect (p=0.04). Similar results were observed when considering the mean change in serum potassium from baseline (proportion of mediation 21.7%, -3.2 to 46.6, p=0.09). In contrast, a smaller proportion of the effect was mediated by serum potassium concentration above 4.0 mmol/L at 5 months after randomization (5.1%, -3.5% to 13.8%, p=0.24).

DISCUSSION

The present study provides valuable pathophysiological and practical insights into the beneficial effects of Eplerenone in optimally-treated patients with heart failure and reduced ejection fraction. In the EMPHASIS-HF study population, a significant proportion of patients were hypokalemic at baseline and during the conduct of the study, a frequently underestimated condition associated with worse outcomes. A minority (approximately 10%) of patients were receiving potassium supplements at baseline. In this setting, based on interaction tests, we show that the MRA Eplerenone was even more protective when administered to optimally-treated patients with HF and reduced ejection fraction with mild symptoms, who were mildly hypokalemic at baseline (3.5 d K^+ < 4 mmol/L: 87% of hypokalemic patients). Moreover, hypokalemia at baseline was associated with worse outcomes only in patients treated with placebo. The relatively high incidence of hypokalemia in the present study suggests that physicians may not be fully aware of the risk associated with mild hypokalemia. One could also suggest that the beneficial effects of MRAs shown herein, beyond their potential pleiotropic effects, may be at least partly mediated by their potassium-sparing properties, as already suggested by our previous results in patients with HF post myocardial infarction[7], and corroborated herein by our mediation sensitivity analysis. Of note, hypokalemia during follow-up was also associated with worse outcomes in multivariable analyses, independently of the major protective effect of Eplerenone.

Hypokalemia is common in patients with HF, in part because of elevated aldosterone levels from neurohormonal activation as well as from the use of diuretics. Accordingly, the use of non-potassium sparing diuretics was found associated herein with hypokalemia both at

baseline and during follow-up. Aldosterone stimulates the exchange of sodium and potassium in distal renal tubules, leading to excretion of potassium in the urine[3]. Potassium is an important determinant of myocardial function, and low serum potassium may cause arrhythmias and sudden cardiac death [5] by accelerating depolarization, increasing automaticity and lengthening the action potential[4, 21, 22]. Serum potassium concentrations <4 mmol/L have previously been associated with increased mortality in the DIG (Digitalis Investigation Group) trial[5, 23 3]. However, in our analysis, the risk associated with hypokalemia remained significant after adjusting for digitalis use (data not shown).

Whether a further up-titration of RAAS inhibitors including MRAs, prone to reset serum potassium concentrations to the potassium range recommended by the American College of Cardiology/American Heart Association guidelines (i.e. 4.0 to 5.0 mmol/l), could further maximize this benefit is an attractive hypothesis and warrants further dedicated studies. Unfortunately, it should be acknowledged that numerous registries have reported a large and persistent gap between real-life practice in the use of life-saving evidence-based therapies (such as RAAS inhibitors, including MRAs) and recommended practices in international guidelines. In any instance, a close monitoring of serum potassium and renal function is essential during these periods of RAAS inhibitor adjustments[1]. Physicians should pay particular attention not only to hyperkalemia but to hypokalemia as well, including in patients with CKD, who are prone to experience adverse outcomes[24], since these patients were found not to be protected from hypokalemia occurrence in the present analysis. In contrast, we previously showed that patients with lower GFR were more prone to experience hyperkalemia whilst receiving MRAs[8] or increased angiotensin receptor blockers doses[25], although the latter did not hinder the clinical benefit of these drugs.

Limitations. First, the present study was a *post-hoc* analysis and included non pre-specified subgroups. Nevertheless, the present data are derived from a substantial randomized controlled trial, thus allowing to reliably assess the association between Eplerenone use, baseline hypokalemia and the primary outcome adjudicated by an endpoint committee. Moreover, a rigorous collection of serum potassium was implemented. Secondly, these results were obtained in patients with HF and reduced ejection fraction, presenting mild symptoms, a serum potassium <5 mmol/L and eGFR >30 ml/min/1.73 m^2 at entry and therefore may not be applicable to patients with HF and preserved ejection fraction. Moreover, there was frequent biochemical monitoring during follow-up as well as implementation of an algorithm to manage hyperkalemia whilst down-titrating the study drug[8]; in addition, there were no prespecified hypokalemia management rules. Therefore, the external validity and potential generalizability to "real world" HF patients is uncertain.

In summary, the present data provide relevant pathophysiological and practical insights, suggesting that in HF patients receiving optimal therapy but not treated with Eplerenone, baseline hypokalemia is associated with worse outcomes. Conversely, hypokalemia amplifies the treatment effect of Eplerenone compared to placebo. Patients with a hypokalemia during follow-up are at increased risk of CV death and/or HF hospitalization and have a better prognosis when treated with Eplerenone compared to others. Greater attention should therefore be paid to screen for even mild hypokalemia in patients with HF, and every effort should be made to correct the latter, under close monitoring of electrolyte balance and kidney function.

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Figure legends

Figure 1

Kaplan-Meier curves of CV death and/or HF hospitalization as a function of treatment in the subgroups of patients with/without baseline $K^+ < 4.0$ mmol/L.

Figure 2: Kaplan-Meier curves of the time to first occurrence of $K^+ < 4.0$ mmol/L during treatment in all study patients.

Aims: Although hypokalemia is common among patients with heart failure (HF), the prognostic significance of baseline hypokalemia and hypokalemia during follow-up in HF patients receiving a mineralocorticoid receptor antagonist (MRA) remains uncertain.

Methods and results: Results of the EMPHASIS-HF trial in patients (n=2737) with HF and reduced ejection fraction with mild symptoms, randomized to Eplerenone or placebo, were analyzed with regard to the presence or occurrence of hypokalemia (serum K^+ <4.0 mmol/L) and the risk of cardiovascular death or hospitalization for HF (primary endpoint). Median follow-up was 21 months.

Baseline hypokalemia and hypokalemia during follow-up were common occurrences (19.6% and 40.6% respectively). Hypokalemia during follow-up was associated with worse outcomes in multivariable analyses (Hazard Ratio (HR) 1.26 (1.05-1.52), p=0.01) without evidence of interaction with Eplerenone. In contrast, baseline hypokalemia was associated with outcomes in the placebo group (HR 1.37, 1.05-1.79, p=0.02) but not in the Eplerenone group (HR 0.87, 0.62-1.23, p=0.44, p for interaction=0.04). Concurrently, Eplerenone was found to be more protective in patients with baseline hypokalemia vs. patients without baseline hypokalemia compared to placebo (HR 0.44 (0.30-0.64), p<0.001 vs. 0.69 (0.57-0.83), p=0.001; p for interaction=0.04). In patients without baseline hypokalemia, Eplerenone use decreased the rate of hypokalemia during follow-up (HR 0.69 (0.59-0.80), p<0.001). A potassium level above 4.0 mmol/L at one month after randomization mediated 26.0% (0.6-51.4%) of the Eplerenone treatment effect (p=0.04).

Conclusion: In HF patients receiving optimal therapy but not treated with Eplerenone, baseline hypokalemia was associated with worse outcomes. Conversely, hypokalemia amplified the treatment effect of Eplerenone.

Figure 1

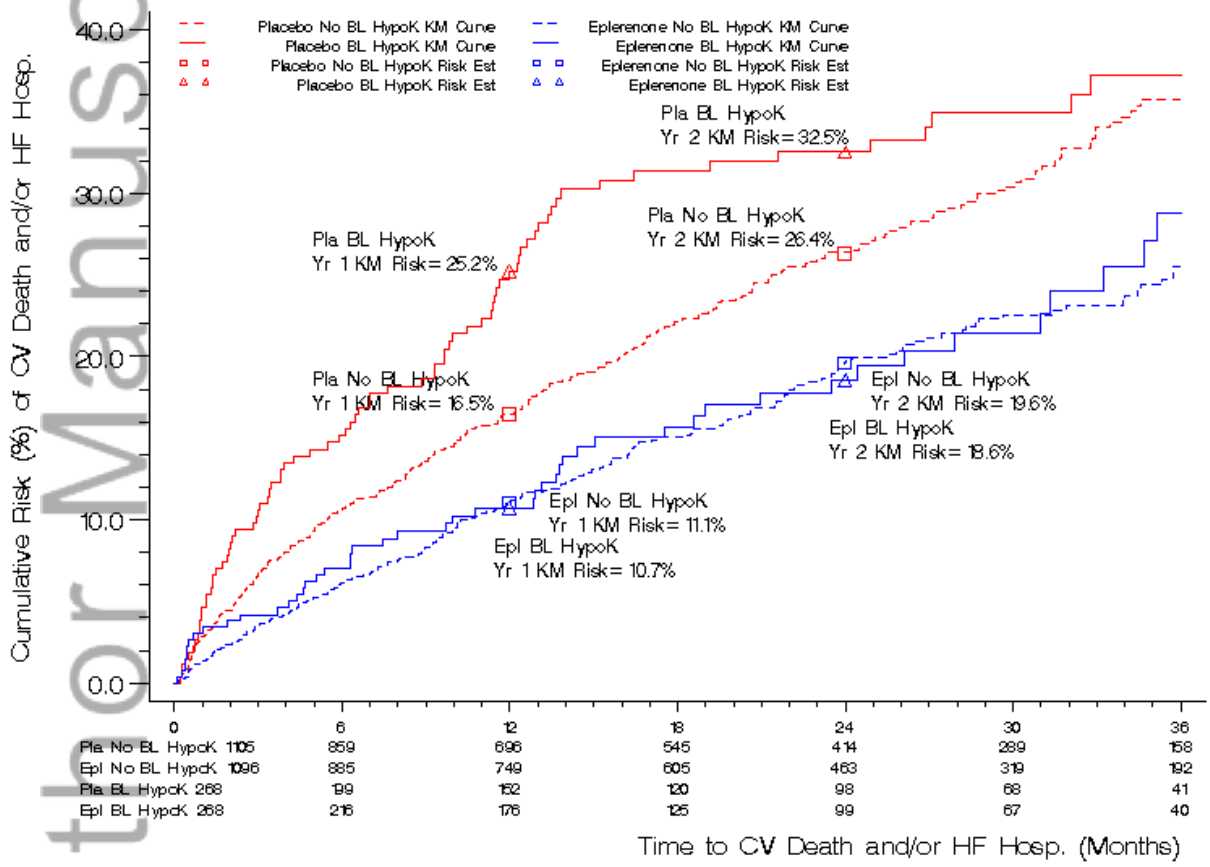
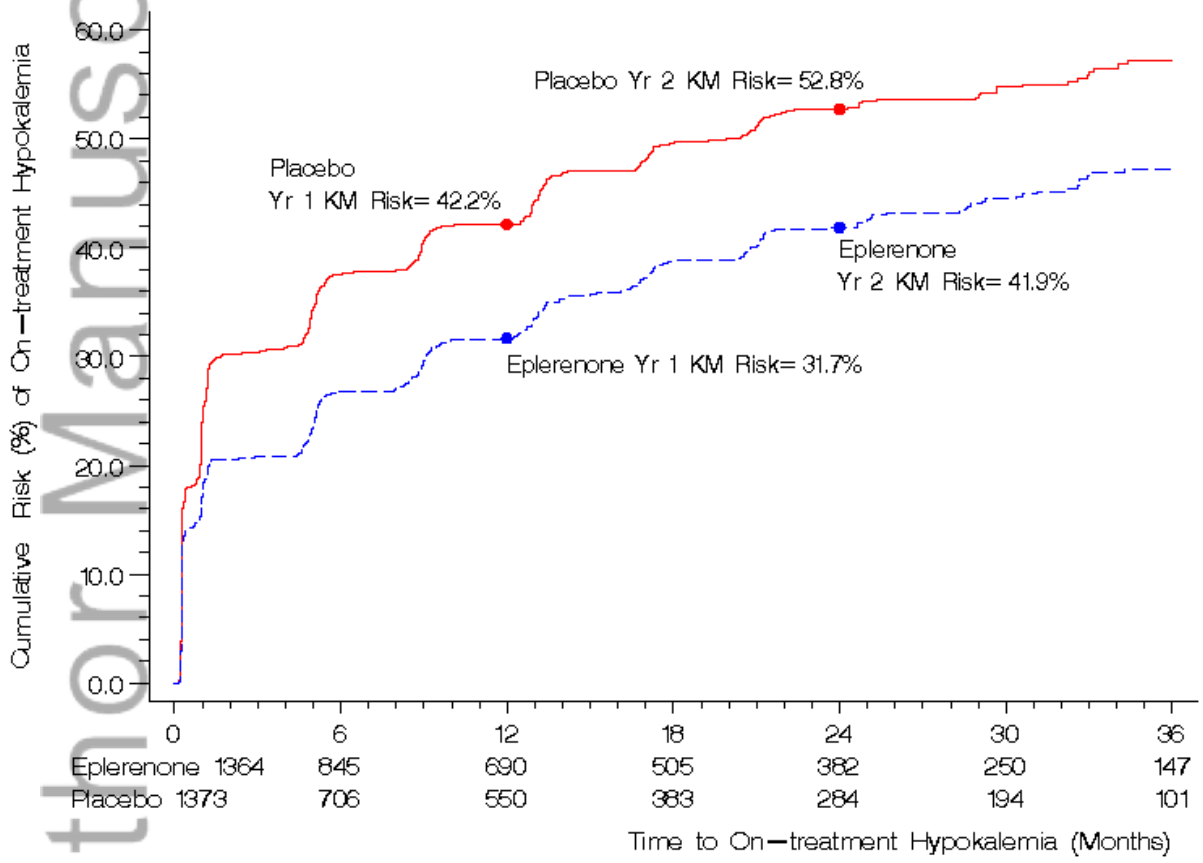


Figure 2: Kaplan-Meier curves of the time to first occurrence of $K^+ < 4.0$ meq/L during treatment in all study patients.



Impact of eplerenone on cardiovascular outcomes in heart failure patients with hypokalemia

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All material is original to the submission

Table 1. Baseline characteristics according to hypokalemia at baseline or during follow-up.

	Baseline hypokalemia			Hypokalemia during follow-up		
	Patients with basal K+ e 4 mmol/l N=2201	Patients with basal K+<4 mmol/l N=536	p-value	No K+<4 during follow-up* N = 1625	At least one K+<4 during follow-up* N = 1112	p-value
Eplerenone	1096 (50%)	268 (50%)	1	870 (54%)	494 (44%)	<0.0001
Demographic/clinical characteristics						
Age (yrs)	69 ± 8	68 ± 8	0.55	69 ± 8	68 ± 8	0.22
Male gender	1729 (79%)	398 (74%)	0.037	1283 (79%)	844 (76%)	0.062
Race						
White	1880 (85%)	388 (72%)	<0.0001	1402 (86%)	866 (78%)	<0.0001
Other	321 (15%)	148 (28%)		223 (14%)	246 (22%)	
Smoking status						
Current smoker	235 (11%)	58 (11%)	0.005			
Past smoker	1014 (46%)	207 (39%)				
Never smoked	952 (43%)	271 (51%)				
Body mass index (kg/m²)	28 ± 5	27 ± 5	0.0004	27.8 ± 5	27.2 ± 5	0.0022
Left ventricular ejection fraction (%)	26.2 ± 5	25.6 ± 5	0.007	26.4 ± 5	25.7 ± 5	<0.0001
Medical history						
Diabetes mellitus	700 (32%)	159 (30%)	0.35	537 (33%)	322 (29%)	0.024
Baseline laboratory parameters						
Estimated GFR (ml/min/1.73m²)	71 ± 22	72 ± 22	0.21	70 ± 21	72 ± 22	0.0045
Baseline medications						
Loop diuretic (%)	1660 (75%)	430 (80%)	0.020	1212 (75%)	878 (79%)	0.009
Loop diuretic (mg/d furosemide equiv.)	64 ± 320	69 ± 71	0.54	67 ± 374	62 ± 57	0.70
Other diuretic (%)	387 (18%)	132 (25%)	0.0003	264 (16%)	255 (23%)	<0.0001
ACE inhibitor, ARB or both (%)	2067 (94%)	490 (91%)	0.041	1529 (94%)	1028 (92%)	0.099
Percent target dose of ACE-I or ARB	59 ± 68	56 ± 51	0.29	59 ± 70	58 ± 58	0.84
Beta-blocker (%)	1929 (88%)	445 (83%)	0.006	1448 (89%)	926 (83%)	<0.0001
Percent target dose of beta blockers	49 ± 102	46 ± 72	0.47	50 ± 106	47 ± 81	0.50
Digitalis glycosides (%)	586 (27%)	154 (29%)	0.33	411 (25%)	329 (30%)	0.014
Potassium supplements (%)	200 (9%)	60 (11%)	0.14	145 (9%)	115 (10%)	0.23

Values are expressed as means ± standard deviation or n (%); p-values were obtained from Student's t-tests or Fisher's exact tests when appropriate.
* Potassium values collected after an occurrence of the primary endpoint were not considered in the determination of hypokalemia during follow-up for this descriptive analysis.
GFR: glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 2: Association between hypokalemia and outcomes and interaction between hypokalemia and Eplerenone treatment effect in multivariable Cox analysis.

	CV death or HFH N= 605 events			CV death N= 332 events		
Effect of hypokalemia in adjusted models*						
Baseline hypokalemia	1.14	0.93-1.41	0.22	1.20	0.91-1.58	0.20
Hypokalemia during follow-up	1.26	1.05-1.52	0.01	1.47	1.16-1.86	0.002
Hypokalemia at 5 months	1.38	1.12-1.71	0.003	1.55	1.18-2.02	0.001
Interaction between baseline hypokalemia and Eplerenone treatment effect in adjusted models*						
Eplerenone treatment effect						
in patients with baseline hypokalemia	0.44	0.30-0.64	<0.0001	0.52	0.32-0.84	0.008
in patients without baseline hypokalemia	0.69	0.57-0.83	0.0001	0.79	0.61-1.03	0.08
Effect of baseline hypokalemia						
in the placebo group	1.37	1.05-1.79	0.02	1.43	1.01-2.03	0.045
in the Eplerenone group	0.87	0.62-1.23	0.44	0.94	0.61-1.44	0.76
	p for interaction=0.04			**p for interaction=0.13**		

***** To ensure uniform adjustment in all Cox models, all relevant variables chosen a priori based on a pathophysiological standpoint were included in 2 interaction models (CV death or HFH and CV death alone). Namely, the following adjustment variables were used: age, gender, ethnicity, BMI, diastolic blood pressure, systolic blood pressure, heart rate, hemoglobin, ejection fraction, diabetes, history of myocardial infarction, history of hospitalization for heart failure, eGFR, use of beta blockers, use of loop diuretics, daily dose of loop diuretics, use of other diuretics, receipt of potassium supplements, use of ACE-I, ARB or both, % of ACE-I or ARB target dose, use of beta blockers, % of beta blocker target dose and use of digitalis.

CV: cardiovascular; HFH: heart failure hospitalization

Table 3: Association of baseline characteristics with hypokalemia during follow-up

	Hypokalemia during follow-up All patients			Incident hypokalemia during follow-up Patients without baseline hypokalemia		
Eplerenone	0.72	0.64-0.81	<0.001	0.69	0.59-0.80	<0.001
Baseline hypokalemia	3.04	2.66-3.47	<0.001	N/A	N/A	N/A
Race (white vs. others)	0.68	0.59-0.80	<0.001	0.72	0.59-0.89	0.002
BMI (for a 1 kg/m² increase)	/	/	/	0.98	0.97-1.00	0.047
LVEF (for a 1% increase)	0.98	0.96-0.99	<0.001	0.97	0.96-0.99	0.0005
Diabetes mellitus	0.86	0.75-0.98	0.03	0.83	0.70-0.98	0.03
Estimated GFR (for a 10 ml/min/1.73m² increase)	/	/	/	1.04	1.01-1.08	0.02
Loop diuretic	1.26	1.08-1.46	0.004	1.28	1.06-1.55	0.01
Other diuretic	1.32	1.14-1.54	<0.001	1.52	1.26-1.83	<0.0001
ACE-I, ARB or both	0.78	0.62-0.98	0.03	/	/	/
Beta-blocker	0.73	0.62-0.86	<0.001	0.69	0.56-0.85	0.0004
Potassium supplements	/	/	/	1.32	1.03-1.69	0.03

BMI: body mass index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

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Potassium supplements	/	/	/	1.32	1.03-1.69	0.03

BMI: body mass index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker