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RESEARCH ARTICLE

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

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Aims Although hypokalaemia is common among patients with heart failure (HF), the prognostic significance of baseline hypokalaemia and hypokalaemia 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 EF with mild symptoms, randomized to eplerenone or placebo, were analysed with regard to the presence or occurrence of hypokalaemia (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 hypokalaemia and hypokalaemia during follow-up were common occurrences (19.6% and 40.6%, respectively). Hypokalaemia during follow-up was associated with worse outcomes in multivariable analyses [hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.05–1.52, $P = 0.01$] without evidence of interaction with eplerenone. In contrast, baseline hypokalaemia was associated with outcomes in the placebo group (HR 1.37, 95% CI 1.05–1.79, $P = 0.02$) but not in the eplerenone group (HR 0.87, 95% CI 0.62–1.23, $P = 0.44$; P for interaction = 0.04). Concurrently, eplerenone was found to be more protective in patients with baseline hypokalaemia vs. patients without baseline hypokalaemia compared with placebo (HR 0.44, 95% 0.30–0.64, $P < 0.0001$ vs. 0.69, 95% CI 0.57–0.83, $P = 0.0001$; P for interaction = 0.04). In patients without baseline hypokalaemia, eplerenone use decreased the rate of hypokalaemia during follow-up (HR 0.69, 95% CI 0.59–0.80, $P < 0.001$). A potassium level >4.0 mmol/L at 1 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 hypokalaemia was associated with worse outcomes. Conversely, hypokalaemia amplified the treatment effect of eplerenone.

Keywords Eplerenone • Heart failure • Potassium • Prognosis

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Introduction

Hypokalaemia 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 hyperkalaemia has hampered the initiation or increase in dosage of these lifesaving drugs in patients with HF and reduced LVEF, who frequently have chronic kidney disease (CKD).[1,2] Previous analyses in patients with HF noted poorer outcomes in those with potassium levels <4.0 mmol/L defining hypokalaemia, while incident hypokalaemia was shown to be attenuated by the use of mineralocorticoid receptor antagonists (MRAs) in patients with NYHA stage III–IV enrolled in the Randomized ALdactone Evaluation Study (RALES).[3–6] We previously reported that, in patients after myocardial infarction with LV dysfunction enrolled in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), an early rise in potassium levels at 1 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 hyperkalaemia, it retained its survival benefits without any significant interaction with the association between hyperkalaemia (>5.5 mmol/L) and worsening renal function and worse outcomes.[8] While hypokalaemia was reported by investigators as an adverse event, hypokalaemia 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 ~0.1 mmol/L after 1 week).[8] Because of protocol-mandated serial monitoring of serum potassium, we were also able to analyse 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 hypokalaemia at baseline or occurring during follow-up in patients enrolled in EMPHASIS-HF. We also assessed the interaction between prevalent hypokalaemia and hypokalaemia 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 h 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 4 weeks and at 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 6-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 1 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

'Hypokalaemia' was defined as a serum potassium <4.0 mmol/L and 'mild hypokalaemia' as $3.5 \leq$ 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 hypokalaemia 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, systolic blood pressure, diastolic blood pressure, heart rate, haemoglobin, EF, diabetes, history of myocardial infarction, history of hospitalization for HF, eGFR, use of ACE inhibitors or ARBs, percentage of ACE inhibitor or ARB target dose, use of beta-blockers, percentage of beta-blocker target dose, use of loop diuretics, daily dose of loop diuretics (furosemide equivalents), use of other diuretics, use of digitalis, and intake of potassium supplements. Analysis was performed either including all covariates in the model or, for other models, using stepwise selection to retain only those covariates shown to be significantly associated with baseline hypokalaemia 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: (i) cardiovascular death or HF hospitalization (primary endpoint); (ii) cardiovascular death; and (iii) occurrence of post-baseline hypokalaemia.

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

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

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

	Baseline hypokalaemia			Hypokalaemia during follow-up		
	Patients with basal K^+ ≥4 mmol/L ($n = 2201$)	Patients with basal K^+ <4 mmol/L ($n = 536$)	*P*-value	No K^+ <4 during follow-up[a] ($n = 1625$)	At least one K^+ <4 during follow-up[a] ($n = 1112$)	*P*-value
Eplerenone	1096 (50%)	268 (50%)	1	870 (54%)	494 (44%)	<0.0001
Demographic/clinical characteristics						
Age (years)	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/m^2)	28 ± 5	27 ± 5	0.0004	27.8 ± 5	27.2 ± 5	0.0022
LVEF (%)	26.2 ± 5	25.6 ± 5	0.007	26.4 ± 5	25.7 ± 5	<0.0001
Diabetes mellitus	700 (32%)	159 (30%)	0.35	537 (33%)	322 (29%)	0.024
eGFR (mL/min/1.7 3 m^2)	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/day furosemide equivalents)	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
Percentage target dose of ACE inhibitor 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
Percentage 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.
eGFR, estimated glomerular filtration rate.
[a]Potassium values collected after an occurrence of the primary endpoint were not considered in the determination of hypokalaemia during follow-up for this descriptive analysis.

The interaction of treatment and hypokalaemia during follow-up on the rates of the primary endpoint was also examined using Cox proportional hazard models similar to those described above. However, for this analysis, hypokalaemia 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 hypokalaemia and the value of 1 thereafter. As a sensitivity analysis, similar Cox proportional hazard analyses were also performed using the incidence of hypokalaemia at Month 5 as the incident hypokalaemia 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 hypokalaemia was estimated by first using the midpoint between the visit at which hypokalaemia 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 hypokalaemia (as defined by a Month 1 level of ≥4.0 mmol/L), mediation analyses were performed using the %MEDIATE

Table 2 Association between hypokalaemia and outcomes and interaction between hypokalaemia and eplerenone treatment effect in multivariable Cox analysis

	CV death or HFH ($n = 605$ events)			CV death ($n = 332$ events)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Effect of hypokalaemia in adjusted models[a]						
Baseline hypokalaemia	1.14	0.93–1.41	0.22	1.20	0.91–1.58	0.20
Hypokalaemia during follow-up	1.26	1.05–1.52	0.01	1.47	1.16–1.86	0.002
Hypokalaemia at 5 months	1.38	1.12–1.71	0.003	1.55	1.18–2.02	0.001
Interaction between baseline hypokalaemia and eplerenone treatment effect in adjusted models[a]						
Eplerenone treatment effect in patients with baseline hypokalaemia	0.44	0.30–0.64	<0.0001	0.52	0.32–0.84	0.008
Eplerenone treatment effect in patients without baseline hypokalaemia	0.69	0.57–0.83	0.0001	0.79	0.61–1.03	0.08
Effect of baseline hypokalaemia in the placebo group	1.37	1.05–1.79	0.02	1.43	1.01–2.03	0.045
Effect of baseline hypokalaemia 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		

CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio.
[a]To ensure uniform adjustment in all Cox models, all relevant variables chosen *a priori* based on a pathophysiological standpoint were included in two interaction models (CV death or HFH and CV death alone). Namely, the following adjustment variables were used: age, gender, ethnicity, body mass index, diastolic blood pressure, systolic blood pressure, heart rate, haemoglobin, EF, diabetes, history of myocardial infarction, history of hospitalization for heart failure, estimated glomerular filtration rate, use of beta-blockers, use of loop diuretics, daily dose of loop diuretics, use of other diuretics, receipt of potassium supplements, use of ACE inhibitors, ARBs, or both, percentage of ACE inhibitor or ARB target dose, use of beta-blockers, percentage of beta-blocker target dose and use of digitalis.

macro developed by Hertzmark *et al.*[12] based on the methods of Lin *et al.*[13]

The macro, applied in patients with baseline hypokalaemia, 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 (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:

$$[1 - (\text{estimate for treatment in model 2} / \text{estimate for treatment in model 1})] \times 100$$

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 (CI) 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% CI 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 hypokalaemia 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 (ORs) and hazard ratios (HRs) are presented with the associated 95% CI 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 data set using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Prevalence and factors associated with baseline hypokalaemia

Patient characteristics according to the presence or absence of baseline hypokalaemia and treatment allocation are described in *Table 1* (and Supplementary material online, *Table S1* for mild baseline hypokalaemia). Overall, baseline hypokalaemia was a common occurrence ($n = 536/2737$, 20%), was mostly mild ($n = 468/536$, 87%), and equally distributed in both the eplerenone and placebo groups. Of note, ~10% of study participants across all subgroups were receiving potassium supplements (*Table 1*; Supplementary material online, *Table S1*).

In multivariable analysis, higher EF (OR 0.98, 95% CI 0.95–1.00, $P = 0.024$), white ethnicity (OR 0.45, 95% CI 0.35–0.58, $P < 0.001$), and history of diabetes (OR 0.78, 95% CI 0.62–0.97, $P = 0.029$) were associated with a lower risk of baseline hypokalaemia. In contrast, higher eGFR (OR 1.06 per 10 unit increase, 95% CI 1.01–1.11, $P = 0.014$), loop diuretic use (OR 1.39, 95% CI 1.07–1.80, $P = 0.014$), and use of other non-potassium-sparing diuretics (OR 1.83, 95% CI 1.43–2.34, $P < 0.001$) were significantly associated with a higher risk of baseline hypokalaemia.

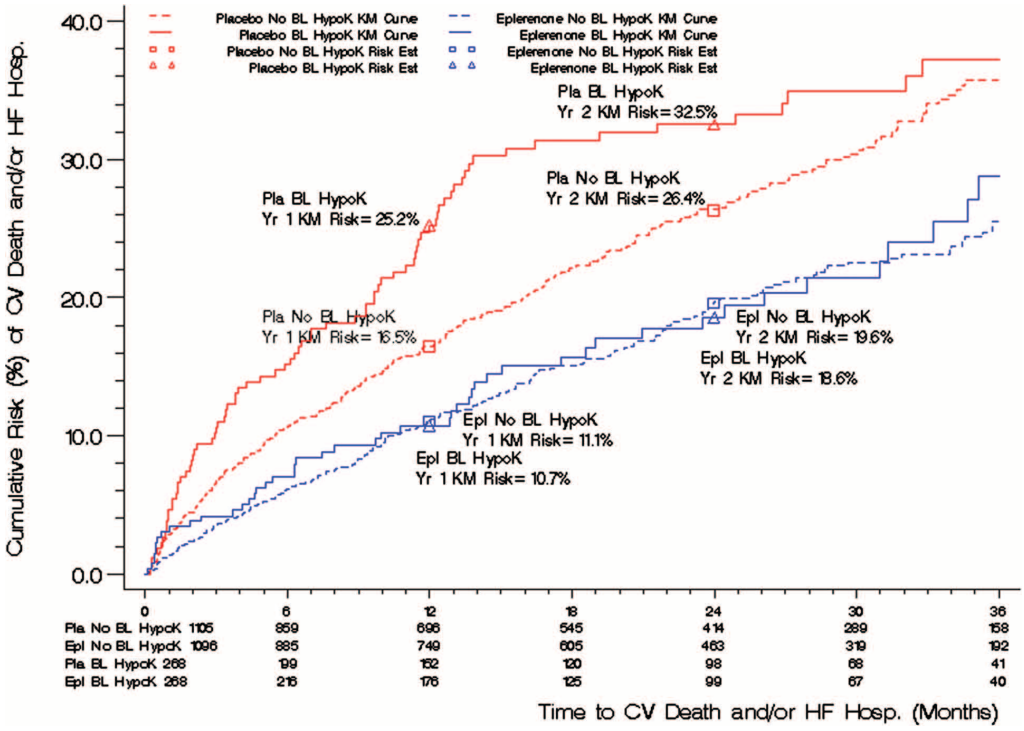

Figure 1 Kaplan–Meier curves of cardiovascular (CV) death and/or heart failure (HF) hospitalization as a function of treatment in the subgroups of patients with/without baseline K^+ <4.0 mmol/L.

Prognostic value of baseline hypokalaemia and interaction with eplerenone

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

Overall, in multivariable analysis, baseline hypokalaemia was not significantly associated with increased rates of the primary outcome (HR 1.14, 95% CI 0.93–1.41, $P = 0.22$) and cardiovascular death (*Table 2*).

Using a multivariable Cox model, a significant interaction was identified between baseline hypokalaemia and eplerenone for the primary outcome (P for interaction = 0.04). Importantly, baseline hypokalaemia was significantly associated with poorer outcome in the placebo group (HR 1.37, 95% CI 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 hypokalaemia (HR 0.44, 95% CI 0.30–0.64, $P < 0.0001$) (*Figure 1*; *Table 2*), a finding also confirmed in a sensitivity analysis encompassing patients with mild baseline hypokalaemia (HR 0.44, 95% CI 0.29–0.65, $P < 0.001$).

Incidence and factors associated with hypokalaemia during follow-up

Overall, hypokalaemia 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 hypokalaemia 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 hypokalaemia during follow-up are depicted in *Table 1*. In multivariable analysis (*Table 3*), eplerenone use was associated with a decreased rate of hypokalaemia during follow-up, while hypokalaemia at baseline was strongly associated with a higher rate of hypokalaemia during follow-up (HR 3.04, 95% CI 2.66–3.47, $P < 0.001$). There was no significant interaction between baseline hypokalaemia and eplerenone with regard to the rate of hypokalaemia during follow-up (P for interaction = 0.40), suggesting that eplerenone had a similar effect on rates of hypokalaemia during follow-up in patients with and without hypokalaemia at baseline. When focusing on patients without hypokalaemia at baseline, higher eGFR, loop diuretics, other diuretics, and potassium supplements were significantly associated with higher rates of hypokalaemia during follow-up, whereas eplerenone was associated with decreased rates of hypokalaemia during follow-up (*Table 3*). Of note, patients with 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 hypokalaemia occurrence (see Supplementary material online, *Figure S1*).

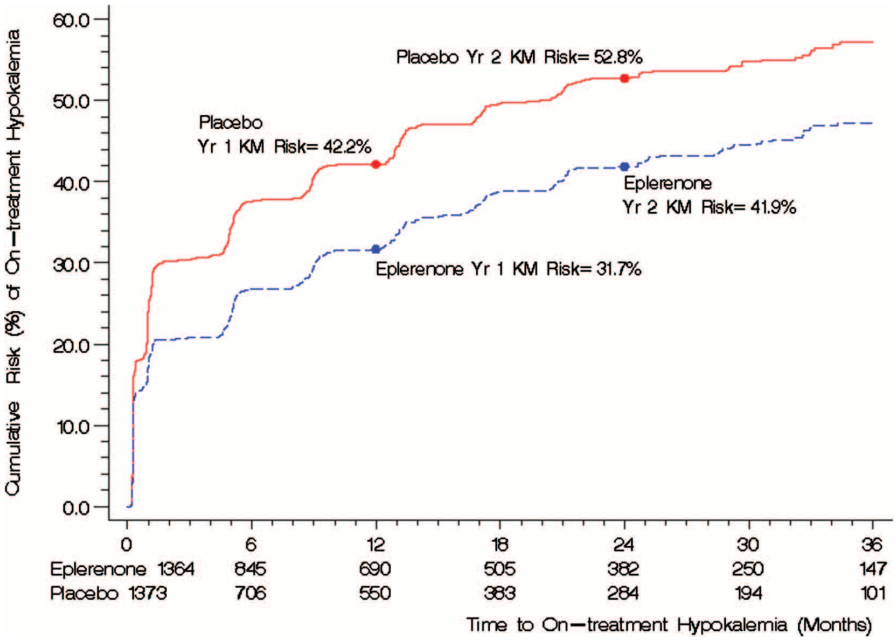

Figure 2 Kaplan–Meier curves of the time to first occurrence of K^+ <4.0 mmol/L during treatment in all study patients.

Prognostic significance of hypokalaemia during follow-up and its interaction with eplerenone treatment

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

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

Mediation sensitivity analysis

In the subset of patients with baseline hypokalaemia, a significantly greater percentage of patients in the eplerenone group exhibited a serum K^+ ≥4.0 mmol/L at Month 1 than in the placebo group [186/268 (69.4%) vs. 138/268 (51.5%), $P < 0.001$]. For most demographics and baseline characteristics, no difference was observed between patients with serum K^+ ≥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^+ ≥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%) vs. 50/82 (61.0%), $P = 0.03$] and in the placebo [111/138 (80.4%) vs. 88/130 (67.7%), $P = 0.02$] groups. In addition, in the eplerenone group, a lower percentage of patients with a serum K^+ ≥4.0 mmol/L at Month 1 were receiving loop diuretics [142/186 (76.3%) vs. 72/82 (87.8%), $P = 0.03$].

Mediation analysis showed that the increase in serum potassium above 4.0 mmol/L at 1 month after randomization mediated 26.0% (0.6–51.4%) 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 >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 HF and reduced EF. In the EMPHASIS-HF study population, a significant proportion of patients were hypokalaemic at baseline and during the conduct of the study, a frequently underestimated condition associated with worse outcomes. A minority (~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 EF with mild symptoms, who were mildly hypokalaemic at baseline ($3.5 \leq K^+ < 4$ mmol/L: 87% of hypokalaemic patients). Moreover, hypokalaemia at baseline was associated with worse outcomes only in patients treated with placebo. The relatively high incidence of hypokalaemia in the present study suggests that physicians may not be fully aware of the risk associated with mild hypokalaemia. One could also suggest that the beneficial effects of

Table 3 Association of baseline characteristics with hypokalaemia during follow-up

	Hypokalaemia during follow-up: all patients			Incident hypokalaemia during follow-up: patients without baseline hypokalaemia		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Eplerenone	0.72	0.64–0.81	<0.001	0.69	0.59–0.80	<0.001
Baseline hypokalaemia	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/m^2 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
eGFR (for a 10 mL/min/1.73 m^2 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 inhibitor, 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; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; N/A, not applicable.

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, hypokalaemia during follow-up was also associated with worse outcomes in multivariable analyses, independently of the major protective effect of eplerenone.

Hypokalaemia 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 herein to be associated with hypokalaemia 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] However, in our analysis, the risk associated with hypokalaemia 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. 4.0–5.0 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 hyperkalaemia but to hypokalaemia 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 hypokalaemia occurrence in the present analysis. In contrast, we previously showed that patients with lower GFR were more prone to experience hyperkalaemia whilst receiving MRAs[8] or increased ARB 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 us to assess reliably the association between eplerenone use, baseline hypokalaemia, 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 EF, 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 EF. Moreover, there was frequent biochemical monitoring during follow-up as well as implementation of an algorithm to manage hyperkalaemia whilst down-titrating the study drug;[8] in addition, there were no pre-specified hypokalaemia 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 hypokalaemia is associated with worse outcomes. Conversely, hypokalaemia amplifies the treatment effect of eplerenone compared with placebo. Patients with a hypokalaemia during follow-up are at increased risk of cardiovascular death and/or HF hospitalization and have a better prognosis when treated with eplerenone compared with others. Greater attention should therefore be paid

to screen for even mild hypokalaemia in patients with HF, and every effort should be made to correct the latter, under close monitoring of electrolyte balance and kidney function.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Kaplan–Meier curves of the time to first occurrence of K^+ <4.0 mEq/L during treatment according to the presence or absence of chronic kidney disease at baseline (i.e. eGFR <60 mL/min/1.73 m^2) in all study patients, in patients treated with eplerenone, or those treated with placebo.

Table S1. Baseline characteristics in patients with $3.5 \leq K^+ < 4$ mmol/L at baseline.

Table S2. Association between hypokalaemia and outcome and interaction between hypokalaemia and eplerenone treatment effect in alternative multivariable Cox analysis excluding treatment variables from adjustment variables.

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