Incidence, Determinants, and Prognostic Significance of Hyperkalemia and Worsening Renal Function in Patients With Heart Failure Receiving the Mineralocorticoid Receptor Antagonist Eplerenone or Placebo in Addition to Optimal Medical Therapy

Results From the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)

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Background—Mineralocorticoid receptor antagonists improve outcomes in patients with systolic heart failure but may induce worsening of renal function (WRF) and hyperkalemia (HK). We assessed the risk factors for mineralocorticoid receptor antagonist–related WRF and for HK, as well as the association between HK and WRF with clinical outcomes in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).

Methods and Results—Serial changes in estimated glomerular filtration rate and in serum potassium were available in 2737 patients during a median 21-month follow-up. HK variably defined as serum K >4.5, 5, or 5.5 mmol/L occurred in 74.7%, 32.5%, and 8.9% patients enrolled in EMPHASIS-HF, respectively. WRF defined as a decrease in estimated glomerular filtration rate >20% or >30% from baseline occurred in 27% and 14% of patients, respectively. Patients assigned eplerenone displayed modest and early but significant and persistent (1) rise in serum potassium and (2) reduction in estimated glomerular filtration rate when compared with those assigned placebo. In multivariate analyses, eplerenone was associated with a higher incidence of WRF and HK, which were interrelated and also associated with baseline patient characteristics (eg, age ≥75 years, hypertension, diabetes mellitus, nonwhite race, ejection fraction <30%, and treatment with an antiarrythmics drug or loop diuretic). Eplerenone retained its survival benefits without any significant interaction with the association between HK >5.5 mmol/L only and WRF and worse outcomes.

Conclusions—In patients with heart failure receiving optimal therapy, WRF and HK were more frequent when eplerenone was added, but their occurrence did not eliminate the survival benefit of eplerenone.

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Key Words: heart failure ■ kidney ■ potassium ■ prognosis

Mineralocorticoid receptor antagonists (MRAs) improve outcomes in patients with systolic heart failure (HF) and mild symptoms. MRAs may induce worsening of renal function (WRF) and hyperkalemia (HK),[1,2] both of which are associated with adverse outcomes.[2–5] More generally, WRF and HK associated with renin angiotensin aldosterone

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system (RAAS) blockade[6,7] are pertaining to physicians and prevent many from appropriately implementing these life-saving drugs in patients with HF.[8] Little is known about the inter-relationships between WRF and HK in patients with HF receiving RAAS inhibitors or the influence these adverse events may have on clinical benefits derived from MRA therapy.

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) investigated the effects of the MRA eplerenone, added to evidence-based therapy including RAAS inhibitors and β-blockers on clinical outcomes, in patients with systolic HF and mild symptoms (ie, New York Heart Association functional class II symptoms). Eplerenone reduced the primary end point of cardiovascular death or HF hospitalization and the secondary end point of all-cause mortality in comparison with placebo when added to evidence-based therapy. HK and WRF were reported as adverse events by investigators. HK was more common in the eplerenone group than in the placebo group (8% versus 3.7%; $P<0.001$).[1] However, HK leading to treatment discontinuation was no more frequent in the eplerenone group (1.1% versus 0.9%; $P=0.57$). The incidence of WRF and the rate of discontinuation because of WRF did not differ between treatment groups.[1] Hospitalization for WRF or HK was adjudicated and neither differed between treatment groups. No death was attributed to WRF or HK. Because of protocol-mandated serial monitoring of serum creatinine and potassium, we have also been able to look at actual changes in renal function and potassium, as opposed to just investigator-reported events. We evaluated the determinants, interactions, and prognostic significance of WRF and HK in patients enrolled in EMPHASIS-HF. We also evaluated the interaction among WRF, HK, and the effect of eplerenone on clinical outcomes.

Table 1. Eplerenone Titration Algorithm Used in EMPHASIS-HF

	Eplerenone Dose
Threshold for eGFR or serum potassium	
eGFR ≥50 mL/min per 1.73 m^2	Start with 25 mg once daily and increased after 4 wk to 50 mg once daily if serum potassium was ≤5 mmol/L
eGFR 30 to 49 mL/min per 1.73 m^2	Start with 25 mg once every other day and increased after 4 wk to 25 mg once daily if serum potassium was ≤5 mmol/L
Guidelines for follow-up (patients monitored) after 1 wk, 1 mo, and every 4 mo thereafter	
Potassium 5.5–5.9 mmol/L at any follow-up time point	Decrease the dose of study drug
Potassium ≥6 mmol/L at any follow-up time point	Withhold study drug and restart only if potassium (remeasured within 72 h) was <5 mmol/L

eGFR indicates estimated glomerular filtration rate; and EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.

Methods

Study Design and Patient Population

The design and main results of the EMPHASIS-HF trial have been reported previously.[9] The study was approved by an institutional review committee, and the subjects gave informed consent. We performed a post hoc analysis in all 2737 patients included in the EMPHASIS-HF trial. Median follow-up was 21 months. Per-protocol dosing requirements based on the estimated glomerular filtration rate (eGFR)[10] and serum potassium are shown in Table 1.[1]

The first objective was to determine the risk associated with HK defined as >4.5, >5, or >5.5 mmol/L (the latter being the cutoff used in the protocol for dose reduction), taking into account the possible occurrence of WRF and eplerenone intake. The incidence and determinants of HK or WRF (defined as a decrease in eGFR >20%[2,11] or >30%[12] from baseline) are also evaluated.

Statistical Analysis

All analyses were performed using SAS version 9.1 software (SAS Institute, Cary, NC). *P* values were 2 sided with statistical significance defined as $P<0.05$. There were no adjustments for multiple comparisons given the post hoc exploratory nature of the analyses. There was no prespecified hierarchical ordering of the analyses.

To examine how serum potassium and eGFR changed over time, repeated-measures ANCOVA models were fit with model terms for treatment group, time point, treatment by time point interaction, and baseline using SAS PROC MIXED. A heterogeneous compound symmetrical covariance structure was fit to the residual error. The adjusted means at each time point were compared between treatment groups using *t* statistics from the repeated-measures model using the DIFF option of the LSMEANS statement. The average annual changes in serum eGFR from baseline to month 29 were calculated for each subject as the slopes of the regression lines using time in years as the independent variable. Summary statistics were calculated, and the mean annual change was compared between treatments using *t* tests. Pearson correlations between serum potassium and eGFR levels were calculated for each time point separately and tested for significance using *t* statistics.

Time-to-event analyses were performed using the Cox regression model. Covariables were entered using a forward selection method, with the final models retaining only the significant factors. In the absence of a clinically prespecified cut point for continuous variables, we chose medians. The validity assumptions of the Cox regression were checked (ie, proportionality of hazards and absence of collinearity or interaction).

Three types of analyses were performed. First, the association of HK with the first occurrence of WRF (as time-dependent covariate) was evaluated, with adjustment for treatment group and ≤4 significant covariates (baseline eGFR, baseline serum potassium, hypertension, and ethnicity) depending on the definition of HK.

Second, the association of WRF with the first occurrence of HK (as time-dependent covariate) was evaluated, with adjustment for treatment group and ≤6 significant covariates (age, baseline eGFR, diabetes mellitus, ejection fraction [EF] <30%, use of antiarrhythmics, and use of diuretics) depending on the definition of WRF.

Third, the association between the first occurrence of HK and WRF (as time-dependent covariates) and 5 clinical outcomes (HF hospitalization/cardiovascular death, HF hospitalization, cardiovascular death, all-cause death, and sudden cardiac death) was evaluated with adjustment for treatment group, and 11 covariates found to be significantly associated with the primary outcome, including age (<75 and ≥75 years), baseline eGFR (≤median and >median), diabetes mellitus, presence of left bundle branch block, sex, mean arterial pressure (≤median and >median), use of potassium supplements, target dose of β-blockers at randomization (<50% and ≥50%), use of antiarrhythmics, use of diuretics, and ethnicity (white versus other). Five additional covariates were tested but not found significant: baseline serum potassium (≤4.5 and >4.5 mmol/L), EF <30%, hypertension, target dose of angiotensin-converting enzyme inhibitor at randomization (<50% and ≥50%), and target dose of angiotensin receptor blocker at randomization (<50% and ≥50%).

Results

Long-Term Effects of Eplerenone on Serum Potassium and on Kidney Function

Compared with placebo, eplerenone induced an early but modest rise in serum potassium (Figure [A]) and decline in eGFR (Figure [B]). Both changes persisted thereafter. The mean (confidence interval) annual rate of change in eGFR was −0.288 mL/min per 1.73 m^2 (−0.395 to −0.182) in the eplerenone group and −0.066 mL/min per 1.73 m^2 (−0.174 to −0.042) in the placebo group (P=0.004 between groups). Throughout the study, eGFR and serum potassium were significantly but weakly negatively correlated (Figure [C]).

Frequency Distributions and Determinants of Increases in Serum Potassium and Worsening Renal Function

HK occurrence at any time during follow-up was common, with 74.7% of patients experiencing serum potassium >4.5 mmol/L (eplerenone, 80%; placebo, 69.4%; P<0.001) and 32.5% with serum potassium >5 mmol/L (eplerenone, 37.9%; placebo, 27.1%; P<0.001). Serum potassium >5.5 mmol/L was less common (8.9%; eplerenone, 11%; placebo, 6.8%; P<0.001). A >20% reduction of eGFR occurred in 27.2% of patients (eplerenone, 30.1%; placebo, 24.4%; P<0.001), and a >30% reduction of eGFR occurred in 14.0% of patients (eplerenone, 16.1%; placebo, 11.9%; P=0.002).

In multivariate analysis, a lower baseline eGFR (below the median of 68 mL/min per 1.73 m^2), serum potassium >4.5 mmol/L at baseline, hypertension, eplerenone treatment group, and the first occurrence of WRF (>20% or 30% decline in eGFR) were independently associated with the development of HK of >5 or >5.5 mmol/L (Table 2). A higher eGFR (greater than the median) at baseline, eplerenone group, and the first occurrence of HK >5 or >5.5 mmol/L were associated with incident WRF (either >20% or >30% decline in eGFR), independent from other predictors in the model, that is, older age, diabetes mellitus, and the use of antiarrhythmic agents (and of diuretics and an EF <30% for WRF >20% only; Table 3).

Eplerenone Exerts a Beneficial Effect on Clinical Outcomes, Independent of HK >5.5 mmol/L or Worsening Renal Function

We performed a multivariate analysis, adjusting for several baseline covariates, including HK, WRF, and eplerenone treatment (Table 4). Sudden cardiac death was not significantly associated with any of these 3 factors and is not discussed further.

Eplerenone was independently and consistently associated with a beneficial effect on all 4 outcomes shown in Table 4. HK was generally not associated with worse outcomes with the exception of potassium >5.5 mmol/L, which was associated with an increased risk of all-cause death. By contrast, the occurrence of WRF was associated with more frequent occurrence of all 4 outcomes regardless of the definition used for WRF. Systematic interaction assessments showed that the effects of eplerenone on outcomes did not significantly change in the setting of HK or WRF regardless of the threshold used to define HK or WRF events (eg, P values of the interaction assessments between 0.31 and 0.72; for the HF hospitalization/cardiovascular death outcome, see the Data Supplement).

Discussion

The present study provides important insights into kidney function and serum potassium variations and their relationship with outcomes in patients with HF, low EF, and mild symptoms treated with RAAS inhibitors. When compared with placebo-treated patients, eplerenone-treated patients exhibited an early, modest, and sustained but statistically significant (1) decline in eGFR and (2) rise in serum potassium. Both HK and WRF were significantly more frequent in the eplerenone group, but eplerenone treatment was only one of several contributors to these biochemical changes. Other independent predictors included older age, baseline eGFR, baseline potassium, hypertension, diabetes mellitus, and antiarrhythmic drug use (Tables 2 and 3). The beneficial effect of eplerenone was consistent (23%–41% improvement in the tested outcomes) and independent of the occurrence of HK and WRF, and no significant interaction with HK and WRF was detected (Data Supplement). A rise in serum potassium at anytime during the study to >5.5 mmol/L was a rare event, occurring in <9% of patients, but it was associated with a higher risk of deaths. A decline in eGFR exceeding 20% or 30% was independently associated with a more frequent occurrence of all clinical outcomes.

These results have major clinical implications. First, eplerenone retained its clinical benefit, despite being associated with more frequent WRF (defined as either a >20% or >30% decline in eGFR) and HK, both of which (HK >5.5 mmol/L) were independently associated with worse outcomes without any significant interaction with eplerenone. This finding suggests that strict adherence to the inclusion criteria, dosing, and monitoring regimens used in EMPHASIS-HF (Table 1) should be applied in clinical practice to realize the positive benefit/risk ratio achieved by eplerenone in the clinical trial. One might also suggest that an increase in serum K^+ >5.5 mmol/L or WRF occurring in patients on eplerenone should prompt closer monitoring of serum K^+ and renal function (eg, at 1 week, 2 weeks, and then monthly for ≥3 months to assure stability). But in view of the beneficial effects of eplerenone on mortality and morbidity, despite the occurrence of HK or WRF, one should consider lowering the dose of eplerenone but not stopping it. Second, these data suggest that a threshold of 5.5 mmol/L may represent a clinically meaningful definition of HK (because this threshold was associated with adverse clinical outcomes; Table 1). This is at variance with the current American College of Cardiology/American Heart Association guidelines stating that serum potassium concentrations should be targeted to <5.0-mEq/L threshold,[13] and the European Society of Cardiology guidelines recommend cautious use with serum potassium >5.0 mmol/L.[14]

Whether even closer monitoring of serum potassium and of eGFR variations from baseline (not only considering eGFR itself because it was performed herein within the titration algorithm) could further improve patient outcomes,

especially in patients with baseline features associated with HK or WRF occurrences (ie, older age ≥75 years, hypertension or diabetes mellitus history, nonwhite race, lower EF <30%, antiarrythmics, and loop diuretic intake), warrants further prospective studies.

This is the first report of the effects of an MRA when compared with placebo on long-term serial changes of both kidney function and serum potassium in patients with chronic HF and mild symptoms. In EMPHASIS-HF, eplerenone induced an early and modest but statistically significant decline in eGFR,

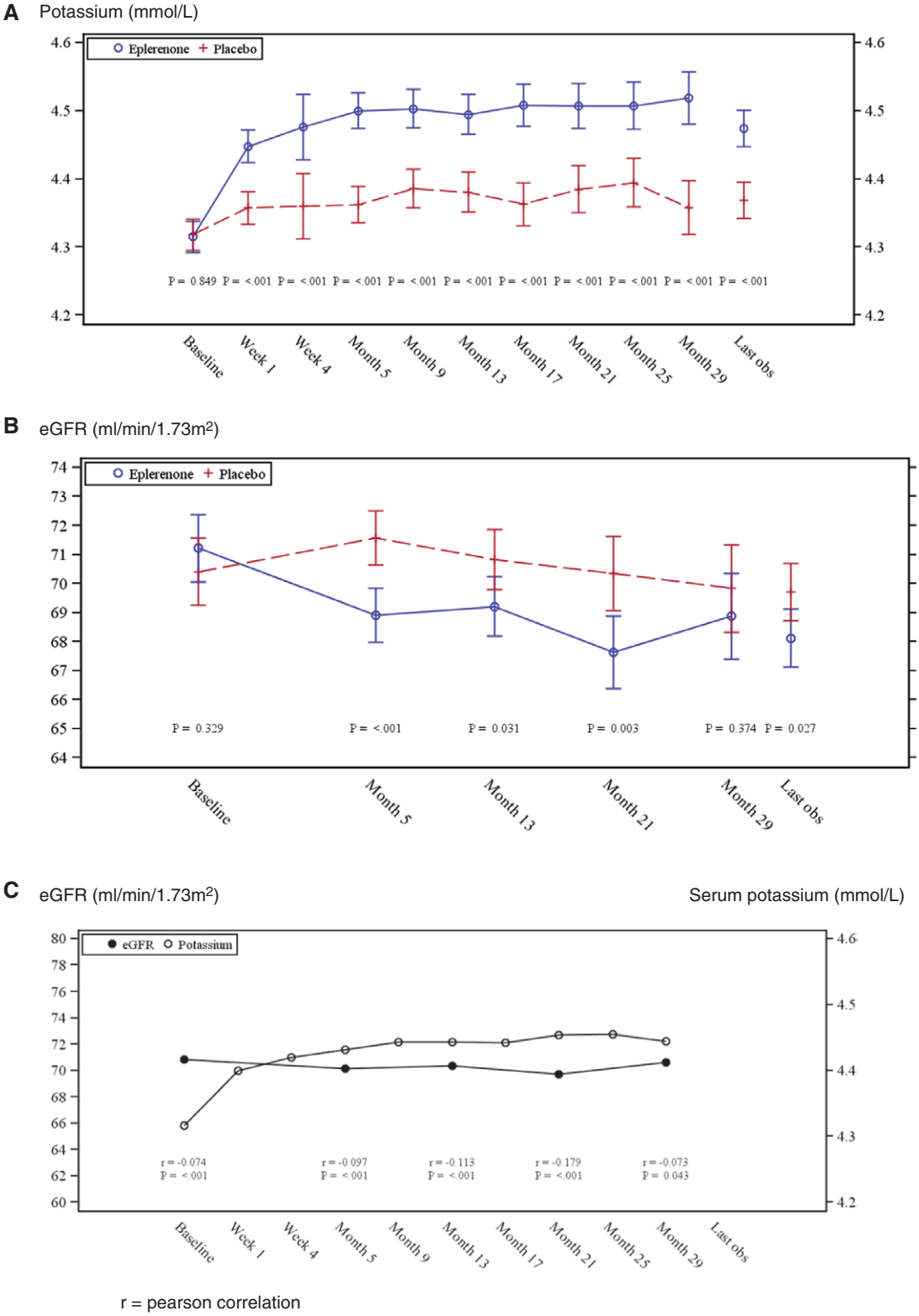

Figure. **A**, Serum potassium (mmol/L) kinetics between treatment groups. **B**, Estimated glomerular filtration rate (eGFR; mL/min per 1.73 m^2) kinetics between treatment groups. **C**, Pearson correlation coefficient of eGFR vs serum potassium by time.

Table 2. Relationship of the Risk of Hyperkalemia With First Occurrence of Worsening Renal Function as Time-Dependant Covariate Using a Multivariate Cox Model Adjusting for Baseline Covariates

	WRF (eGFR Decrease >20%)			WRF (eGFR Decrease >30%)		
	HK>4.5	HK>5.0	HK>5.5	HK>4.5	HK>5.0	HK>5.5
Events/Patients	1959/2624	881/2711	243/2734	1959/2624	881/2711	243/2734
WRF	1.21 (0.95–1.55)	1.58 (1.27–1.97)	2.23 (1.56–3.19)	1.53 (1.09–2.15)	1.45 (1.07–1.97)	2.47 (1.61–3.78)
	P=0.13	*P*<0.001	*P*<0.001	*P*=0.015	*P*=0.015	*P*<0.001
BL eGFR ≤ median (68 mL/min per 1.73 m^2)	NA	1.28 (1.12–1.46)	1.77 (1.36–2.30)	NA	1.26 (1.10–1.44)	1.73 (1.33–2.25)
		P<0.001	*P*<0.001		*P*<0.001	*P*<0.001
BL K> 4.5 mmol/L	NA	2.42 (2.12–2.76)	2.56 (1.98–3.31)	NA	2.41 (2.11–2.75)	2.54 (1.96–3.28)
		P<0.001	*P*<0.001		*P*<0.001	*P*<0.001
Hypertension	NA	1.23 (1.06–1.42)	1.69 (1.25–2.29)	NA	1.23 (1.06–1.42)	1.7 (1.26–2.30)
		P=0.006	*P*<0.001		*P*=0.006	*P*<0.001
Eplerenone	1.28 (1.17–1.40)	1.51 (1.32–1.73)	1.67 (1.29–2.17)	1.28 (1.17–1.40)	1.51 (1.32–1.73)	1.67 (1.29–2.16)
	P<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001
White ethnicity	NA	NA	0.71 (0.50–1.00)	NA	NA	0.71 (0.50–1.01)
			P=0.052			*P*=0.055

Values are hazard ratio (95% confidence interval) and *P* value. BL indicates baseline; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; K, kalemia; NA, not applicable; and WRF, worsening renal function.

which is consistent with our previous observations from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS).[2] A similar eGFR kinetics was observed generally in patients with more severe HF enrolled in Randomized ALdactone Evaluation Study (RALES).[12] A functional hemodynamic effect because of blockade of the RAAS is presumably involved[15] in the early eGFR decline observed in the 3 MRA studies because no further subsequent deterioration occurred over time.

In the present study, we report that, under close monitoring, episodes of WRF were common during follow-up and were associated with higher mortality and hospitalization rates. This finding is consistent with previous reports showing that WRF during hospitalization or shortly after discharge is a major independent risk factor for mortality in patients with postinfarction left ventricular dysfunction and HF, as shown in the SAVE (Survival and Ventricular Enlargement), VALIANT (VALsartan In Acute myocardial iNfarcTion), and EPHESUS

Table 3. Relationship of Risk of Worsening Renal Function With First Occurrence of Hyperkalemia as Time-Dependant Covariate: Multivariate Cox Model Adjusting for Baseline Covariates

	HK>4.5 mmol/L		HK>5.0 mmol/L		HK>5.5 mmol/L	
	WRF (>20%)	WRF (>30%)	WRF (>20%)	WRF (>30%)	WRF (>20%)	WRF (>30%)
Events/Patients	745/2736	384/2736	745/2736	384/2736	745/2736	384/2736
Hyperkalemia	1.00 (0.85–1.18)	1.26 (0.99–1.61)	1.24 (1.05–1.46)	1.67 (1.35–2.07)	1.37 (1.03–1.82)	1.51 (1.06–2.16)
	P=1.00	*P*=0.064	*P*=0.011	*P*<0.001	*P*=0.029	*P*=0.024
Age ≥75 y	1.54 (1.31–1.81)	1.70 (1.37–2.12)	1.55 (1.32–1.82)	1.72 (1.38–2.15)	1.54 (1.31–1.82)	1.70 (1.36–2.12)
	P<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001
BL eGFR ≤median (68 mL/min per 1.73 m^2)	0.60 (0.52–0.70)	0.70 (0.57–0.87)	0.60 (0.51–0.70)	0.69 (0.56–0.85)	0.60 (0.51–0.70)	0.70 (0.57–0.86)
	P<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001
Diabetes mellitus	1.41 (1.22–1.64)	1.43 (1.16–1.76)	1.40 (1.21–1.63)	1.40 (1.13–1.72)	1.41 (1.22–1.64)	1.43 (1.16–1.76)
	P<0.001	*P*<0.001	*P*<0.001	*P*=0.002	*P*<0.001	*P*<0.001
Ejection fraction <30%	1.19 (1.01–1.40)	NA	1.19 (1.01–1.40)	NA	1.19 (1.01–1.40)	NA
	P=0.038		*P*=0.039		*P*=0.040	
Eplerenone	1.22 (1.06–1.42)	1.28 (1.05–1.57)	1.21 (1.04–1.39)	1.26 (1.03–1.54)	1.21 (1.05–1.40)	1.29 (1.06–1.59)
	P=0.006	*P*=0.016	*P*=0.012	*P*=0.026	*P*=0.009	*P*=0.013
Antiarrthymics	1.34 (1.10–1.64)	1.39 (1.06–1.84)	1.34 (1.10–1.65)	1.40 (1.06–1.85)	1.34 (1.10–1.64)	1.40 (1.06–1.85)
	P=0.004	*P*=0.018	*P*=0.004	*P*=0.016	*P*=0.004	*P*=0.017
Diuretics	1.27 (1.03–1.57)	NA	1.28 (1.04–1.58)	NA	1.27 (1.02–1.56)	NA
	P=0.027		*P*=0.022		*P*=0.029	

Values are hazard ratio (95% confidence interval) and *P* value. BL indicates baseline; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; NA, not applicable; and WRF, worsening renal function.

Table 4. Relationship of Risk of Hyperkalemia, Worsening Renal Function, and Treatment Group With Clinical Outcomes Using a Multivariate Cox model Adjusting for Baseline Covariates

	HF Hospitalization/CV Death (n/N, 604/2736)	HF Hospitalization (n/N, 417/2736)	CV Death (n/N, 331/2736)	All-Cause Death (n/N, 383/2736)
HK>4.5 mmol/L	0.86 (0.72–1.03)	0.86 (0.69–1.06)	0.80 (0.63–1.01)	0.83 (0.66–1.03)
WRF>20%	1.30 (1.03–1.63)	1.43 (1.09–1.88)	1.34 (1.01–1.77)	1.38 (1.07–1.78)
EPL	0.64 (0.55–0.76)	0.60 (0.49–0.73)	0.77 (0.62–0.95)	0.77 (0.63–0.95)
HK>5.0 mmol/L	1.08 (0.90–1.31)	0.97 (0.77–1.23)	1.08 (0.85–1.39)	1.07 (0.85–1.35)
WRF>20%	1.28 (1.02–1.61)	1.42 (1.08–1.87)	1.31 (0.99–1.74)	1.36 (1.05–1.75)
EPL	0.63 (0.54–0.74)	0.59 (0.48–0.72)	0.74 (0.60–0.93)	0.75 (0.61–0.92)
HK>5.5 mmol/L	1.20 (0.89–1.61)	1.10 (0.76–1.60)	1.37 (0.95–1.98)	1.40 (1.01–1.96)
WRF>20%	1.28 (1.02–1.61)	1.41 (1.07–1.86)	1.31 (0.99–1.73)	1.35 (1.04–1.74)
EPL	0.63 (0.54–0.74)	0.59 (0.48–0.72)	0.74 (0.59–0.92)	0.75 (0.61–0.91)
HK>4.5 mmol/L	0.86 (0.72–1.03)	0.86 (0.69–1.06)	0.79 (0.62–1.01)	0.82 (0.65–1.03)
WRF>30%	1.55 (1.17–2.07)	1.43 (0.99–2.05)	1.53 (1.08–2.16)	1.69 (1.24–2.30)
EPL	0.64 (0.54–0.76)	0.60 (0.49–0.73)	0.77 (0.61–0.95)	0.77 (0.63–0.94)
HK>5.0 mmol/L	1.08 (0.89–1.30)	0.98 (0.77–1.23)	1.08 (0.84–1.38)	1.07 (0.85–1.34)
WRF>30%	1.52 (1.14–2.02)	1.41 (0.98–2.03)	1.49 (1.05–2.10)	1.65 (1.21–2.25)
EPL	0.63 (0.53–0.74)	0.59 (0.49–0.72)	0.74 (0.60–0.92)	0.75 (0.61–0.92)
HK>5.5 mmol/L	1.19 (0.88–1.60)	1.11 (0.76–1.60)	1.36 (0.95–1.97)	1.39 (0.99–1.94)
WRF>30%	1.51 (1.13–2.01)	1.40 (0.97–2.01)	1.47 (1.04–2.08)	1.63 (1.20–2.22)
EPL	0.63 (0.53–0.74)	0.59 (0.48–0.72)	0.74 (0.59–0.92)	0.74 (0.61–0.91)

Adjusted for treatment group, age (<75 and ≥75 y), baseline estimated glomerular filtration rate (≤median and >median), diabetes mellitus, presence of left bundle branch block, sex, mean arterial pressure (≤median and >median), use of potassium supplements, target dose of β-blockers at randomization (<50% and ≥50%), use of antiarrhythmics, use of diuretics, and ethnicity (white vs other). Values are hazard ratio (95% confidence interval). CV indicates cardiovascular; EPL, eplerenone vs placebo; HF, heart failure; HK, hyperkalemia; and WRF, worsening renal function from baseline.

trials.[2,16,17] Similarly, a meta-analysis of 8 studies representing 18 634 patients showed that an increase in serum creatinine >0.2 mg/dL (17.6 μmol/L) or a corresponding decrease in eGFR >5 mL/min per 1.73 m^2 was associated with a 62% increase in mortality in both in-hospital patients and ambulatory patients.[4] However, all previous reports were focused on the prognostic significance of WRF considered separately from HK. Importantly, we show for the first time that the occurrence of WRF (defined as a >20% or >30% decrease in eGFR) is associated with adverse outcomes independently from HK.

Patients with HF are particularly susceptible to HK because the reduction in renal function frequently associated with HF, older age, and comorbidities, such as diabetes mellitus and RAAS blockade hampers baseline potassium excretion.[18,19] In an analysis of patients enrolled in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program in which a broad spectrum of patients with HF were randomized to treatment with candesartan or placebo in addition to optimal medical therapy, Desai et al[18] identified age, diabetes mellitus, renal dysfunction (creatinine ≥2.0 mg/dL), starting serum potassium ≥5.0 mEq/L, background therapy with angiotensin-converting enzyme inhibitor or spironolactone, and randomization to the angiotensin receptor blocker as multivariable predictors of clinically important HK. In an EPHESUS post hoc analysis, 4 independent baseline predictors of HK (defined as ≥6.0 mEq/L) were identified: baseline potassium greater than the median (4.3 mEq/L), baseline eGFR ≤60 mL/min per 1.73 m^2, history of diabetes mellitus, and previous use of antiarrhythmic agents. None of these independent baseline risk factors significantly affected the cardiovascular benefit of eplerenone for reducing all-cause mortality.[19] In the present study, a history of hypertension, eplerenone use, higher baseline serum potassium concentrations (>4.5 mmol/L) and lower baseline eGFR (as well as nonwhite ethnicity for HK >5.5 mmol/L), and WRF onset were identified as independent predictors of the occurrence of HK >5 and >5.5 mmol/L. Furthermore, HK >5.5 mmol/L was an independent predictor of outcomes, even after adjustment for baseline predictors of WRF and HK and the occurrence of WRF.

The occurrence of HK or of WRF did not hinder the major clinical benefits of eplerenone most likely because of the careful management of rises in potassium, dosing algorithm, and serum potassium and creatinine monitoring regimen used in the present clinical trial that are, therefore, to be strongly

recommended in clinical practice to retrieve the positive benefit/risk ratio achieved by eplerenone in EMPHASIS-HF. This happened even in subgroups of patients at high risk of HK or WRF (ie, patients ≥75 years, with diabetes mellitus, with eGFR<60 mL/min per 1.73 m^2, and with systolic blood pressure <median of 123 mm Hg).[20] Interestingly, in patients with HF enrolled in RALES although WRF during the titration phase (WRF occurring later being not studied herein) occurred more frequently in patients randomized to spironolactone, the risk associated with this worsening was greatest in patients in the placebo group and was markedly attenuated in those taking spironolactone.[12] Therefore, the present EMPHASIS-HF analysis, considering the occurrences of HK and WRF (with several cutoffs used), anytime corroborate and expand our previous conclusions.

Limitations

First, our analysis was post hoc. However, the present data were derived from a large randomized controlled trial with rigorous collection of serum creatinine, serum potassium, and clinical events adjudicated by an end point committee. These results were obtained in patients with HF and a reduced EF, mild symptoms, and serum potassium <5 mmol/L, eGFR >30 mL/min per 1.73 m^2 at entry; there was frequent biochemical monitoring during follow-up. Therefore, the external validity and potential generalizability to real-world patients with HF is uncertain. Importantly, however, the determinants of WRF and HK in EMPHASIS-HF were similar to those identified in other HF populations. Finally, the present results were based on estimated GFR, using the MDRD (Modification of Diet in Renal Disease) formula, which accurately estimates kidney function in patients with HF,[21] with an eGFR <60 mL/min per 1.73 m^2 but maybe not in others.

Conclusions

In summary, our data provide critical practical insights into long-term cardiorenal interactions and outcomes in patients with left ventricular systolic dysfunction with mild symptoms receiving RAAS inhibitor and MRA therapy. Episodes of HK or WRF were common in patients receiving optimal therapy, including angiotensin-converting enzyme inhibitor or angiotensin receptor blockers and β-blockers. The addition of eplerenone increased the rate of WRF and HK. Both types of adverse events may pose a therapeutic dilemma in daily practice because the patients at highest risk for these complications are the patients who derive the greatest absolute cardiovascular benefit from RAAS inhibitors and MRAs.[7] However, and most importantly, these adverse outcomes did not negate the major survival benefit of eplerenone when electrolyte and kidney function were systematically monitored, and eplerenone doses were adjusted based on renal function and potassium concentration.

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CLINICAL PERSPECTIVE

Episodes of hyperkalemia or worsening renal function were common in patients with systolic heart failure and mild symptoms receiving optimal therapy, including angiotensin-converting enzyme inhibitor or angiotensin receptor blockers and β-blockers. The addition of eplerenone increased the rate of worsening renal function and hyperkalemia. Both types of adverse events may pose a therapeutic dilemma in daily practice because the patients at highest risk for these complications are the patients who derive the greatest absolute cardiovascular benefit from renin angiotensin aldosterone system inhibitors, including mineralocorticoid receptor antagonists. However, and most importantly, these adverse outcomes did not negate the major survival benefit of eplerenone, when electrolyte and kidney function were systematically monitored, and eplerenone doses were adjusted based on renal function and potassium concentration.

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SUPPLEMENTAL MATERIAL
Supplemental data on Table 4: interactions with treatment group

Supplemental Table 4A: Multivariate cox model adjusting for baseline covariates**:** Relationship of risk of HF hospiltalization/CV death with HK and WRF (eGFR decrease>20%): tests for HK by risk factor interactions*

		K>4.5 mmol/L		K>5.0 mmol/L		K>5.5 mmol/L	
risk factor	category	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value
treatment group	placebo	---	0.485	---	0.466	---	0.320
	eplerenone	---		---		---	

* HK and WRF as time dependent covariates adjusted for risk factors

Supplemental Table 4B: Multivariate cox model adjusting for baseline covariates: Relationship of risk of HF hospitalization/CV death with HK and WRF (eGFR decrease>30%): tests for HK by risk factor interactions*

		K>4.5 mmol/L		K>5.0 mmol/L		K>5.5 mmol/L	
risk factor	category	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value
treatment group	placebo	---	0.530	---	0.563	---	0.373
treatment group	eplerenone	---		---		---	

* HK and WRF as time dependent covariates adjusted for risk factors

Supplemental Table 4C: Multivariate cox model adjusting for baseline covariates **:** Relationship of risk of HF hospitalization/cv death with HK and WRF(eGFR decrease>20%): tests for WRF by risk factor interactions*

		K>4.5 mmol/L		K>5.0 mmol/L		K>5.5 mmol/L	
risk factor	category	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value
treatment group	placebo	---	0.337	---	0.314	---	0.308
	eplerenone	---		---		---	

* HK and WRF as time dependent covariates adjusted for risk factors

Supplemental Table 4D: Multivariate cox model adjusting for baseline covariates**:** Relationship of risk of HF hospitalization/CV death with HK and WRF(eGRF decrease>30%): tests for WRF by risk factor interactions*

		K>4.5 mmol/L		K>5.0 mmol/L		K>5.5 mmol/L	
risk factor	category	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value	HR (95% ci)	interaction p value
treatment group	placebo	---	0.725	---	0.716	---	0.699
	eplerenone	---		---		---	

* HK and WRF as time dependent covariates adjusted for risk factors