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Serum sodium and eplerenone use in patients with a myocardial infarction and left ventricular dysfunction or heart failure: insights from the EPHESUS trial

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Abstract

***Background*:** Sodium changes are common in myocardial infarction (MI) complicated with left ventricular systolic dysfunction (LVSD) and/or heart failure (HF). Sodium handling is fine-tuned in the distal nephron, were eplerenone exhibits some of its pleotropic effects. Little is known about the effect of eplerenone on serum sodium and the prognostic relevance of sodium alterations in patients with MI complicated with LVSD and/or HF.

Methods: The EPHESUS trial randomized 6632 patients to either eplerenone or placebo. Hyponatremia and hypernatremia were defined as sodium <135 mmol/L or >145 mmol/l respectively. Linear mixed models and time-updated Cox regression analysis were used to determine the effect of eplerenone on sodium changes and the prognostic importance of sodium changes, respectively. The primary outcomes were all-cause mortality and a composite of cardiovascular (CV) mortality and CV-hospitalization.

***Results*:** A total of 6221 patients had a post-baseline sodium measurement, 797 patients developed hyponatremia (mean of 0.2 events/per patient) and 1476 developed hypernatremia (mean of 0.4 events/per patient). Patients assigned to eplerenone had a lower mean serum sodium over the follow-up (140 vs 141mmol/L; p<0.0001) and more often developed hyponatremia episodes (15% vs 11%; p=0.0001) and less often hypernatremia episodes (22% vs. 26% p=0.0003). Hyponatremia, but not hypernatremia was associated with adverse outcome for all outcome endpoints in the placebo group but not in the eplerenone group (Interaction p-value<0.05 for all). Baseline sodium values did not influence the treatment effect of eplerenone in reducing the various endpoints (interaction p-value >0.05 for all). Development of new-onset hyponatremia following eplerenone initiation did not diminish the beneficial eplerenone treatment effect.

***Conclusion*:** Eplerenone induces minor reductions in serum sodium. The beneficial effect of eplerenone was maintained regardless of the baseline serum sodium or the development of hyponatremia. Sodium alterations should not refrain clinicians from prescribing eplerenone to patients who had an MI complicated with LVSD and/or HF.

Key-words: myocardial infarction; heart failure; systolic dysfunction; eplerenone; hyponatremia;; hypernatremia; electrolytes.

ClinicalTrials.gov identifier: NCT00232180

Introduction

Sodium changes are frequently encountered in patients with cardiovascular disease, especially in patients with an acute myocardial infarction and/or heart failure.(1-13) Both in the setting of a myocardial infarction or heart failure, hyponatremia is associated with increased mortality and morbidity. However it is uncertain whether hyponatremia is just a risk marker of more advanced disease or also directly contributes to adverse outcome.(6)

Serum sodium concentrations are mainly regulated at the level of distal nephron, where tubular flow, distal sodium reabsorption and the relative permeability to free water of the collecting ducts determine ultimate urine tonicity and serum sodium concentration.(14) Mineralocorticoid receptor antagonists (MRA), by inhibiting the aldosterone-sensitive sodium channels, result in less reabsorption of sodium in the distal nephron. As a result, MRAs hamper the ability of the distal nephron to generate maximal dilute urine, which could worsen hyponatremia.

Guidelines give a strong recommendation (class IA) for the use of MRAs in selected patients with a recent myocardial infarction and systolic dysfunction or heart failure.(15, 16) However, little information is available about the impact of MRA use on serum sodium levels and the potential prognostic meaning of treatment induced sodium changes. The current post-hoc analysis of the EPHESUS (Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction)(17) trial aims to determine; (1) the effect of eplerenone on serum sodium levels, (2) the prognostic relevance of sodium changes and, (3) the interaction between sodium and the treatment effect of eplerenone in patients with an acute myocardial infarction complicated with left ventricular systolic dysfunction and/or HF.

Methods

Study design and population

The methodology and the results of the EPHESUS study (NCT00232180) have been previously described.(17) Briefly, Patients enrolled in EPHESUS had an acute myocardial infarction complicated by systolic dysfunction (left ventricular ejection fraction ≤40%), heart failure (documented by at least one of the following: presence of pulmonary rales, chest radiography showing pulmonary venous

congestion, or the presence of a third heart sound) or diabetes. Patients were enrolled in the trial 3-14 days after the myocardial infarction and were randomly assigned to treatment with eplerenone or placebo in a 1:1 fashion in addition to receiving standard medical therapy, which could include angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), β-blockers, diuretics, aspirin, statins as well as coronary reperfusion therapy. EPHESUS was an event-driven study with a mean follow-up duration of 16 months. The study was performed according to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Definition of sodium alterations at follow-up

Patients were followed up after randomization at one week, four weeks, three months and every three months there-after. Sodium analysis were performed by protocol at baseline, at 3 months, 6 months, 12 months, 18 months and 24 months of follow-up. To determine the development of sodium alterations after randomization, new onset hyponatremia was defined as any post-baseline sodium <135 mmol/L for patients with a baseline sodium value of ≥135mmol/L. New onset hypernatremia was defined as any post-baseline sodium value >145 mmol/L together with a baseline sodium value ≤145mmol/L. For patients with a post-baseline sodium measurement falling into the category of both new onset hyponatremia and new onset hypernatremia, the last available sodium measurement was used for categorization.

Outcome endpoints

In line with the original report of the EPHESUS trial, the two primary endpoints were; **(1)** all-cause mortality and **(2)** a composite of cardiovascular mortality or cardiovascular hospitalization The secondary endpoints were; **(1)** cardiovascular mortality and **(2)** a composite of all-cause mortality or all-cause hospitalization. For the manuscript an exploratory endpoint was designed consisting of: **(1)** a composite of cardiovascular mortality or heart failure hospitalization (HFH) and **(2)** HFH alone. All endpoints in the EPHESUS trial were adjudicated by an independent and blinded endpoint committee.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies (percentages). Between groups assessment of categorical variables were compared using Pearson's Chi-2 test or Fisher's exact, while continuous variables were compared using student t test. Linear mixed effects models with repeated measures over time were performed to assess changes in serum sodium levels over time according to treatment group allocation (eplerenone vs. placebo). The baseline sodium and the interaction of the treatment by time were specified as fixed effects and the patient level as a random effect (to model the intrinsic patient related covariance between visits within one patient). Multivariable logistic regression models were used to determine if eplerenone treatment assignment is an independent predictor for developing hyponatremia and hypernatremia. Cox regression models with time updated covariate structures of serum sodium were used to assess the relation between sodium changes and the primary, secondary and tertiary endpoints. Hazard ratios (HR) are presented with their 95% confidence interval (CI). Time updated serum sodium values, visualized as B-splines, were tested in outcome analysis after covariate adjustment. Covariates were chosen based on clinical relevance, prognostic importance and use in previous post-hoc analysis in the EPHESUS-trial.(18) Covariates for adjustment included: age, sex, Killip class, left ventricular ejection fraction, reperfusion therapy, hemoglobin, potassium (time updated), systolic blood pressure, heart rate, estimated glomerular filtration rate calculated by CKD-Epi formula (time updated), body mass index, history of diabetes, history of hypertension, history atrial fibrillation, history of chronic obstructive pulmonary disease, previous myocardial infarction, previous HFH, peripheral arterial disease, use of diuretics, ACEi/ARB, Beta-blocker, digoxin and eplerenone assignment. In addition to modeling sodium as a continuous variable (B-spline), sodium was also modeled categorically as new-onset hypo- and hypernatremia. To determine the impact of sodium levels on the treatment effect of eplerenone, treatment interaction was assessed (sodium*treatment interaction) for the different endpoints, using both baseline sodium and the categories of post baseline sodium alterations with reporting of p-values for interaction. The treatment effect of eplerenone was visually depicted over the entire serum sodium range. All analyses were performed using SAS version 9.4.

Results

Characteristics of the study population

Of the 6632 patients included in the EPHESUS trial, 6221 patients had a post-baseline sodium measurement and were included in the current analysis. Baseline features of patients with versus without a post-baseline sodium are shown in supplemental table 1. At baseline, before treatment assignment, 625 patients (10%) had hyponatremia and 402 patients (6%) had hypernatremia.

During a median follow-up of 16 (12-21) months a total of 733 patients developed new onset hyponatremia (mean of 0.2 hyponatremia events per patient, range 0-6 events) and 1399 developed new onset hypernatremia (mean of 0.4 hypernatremia events per patient, range 0-8 events). Baseline characteristics of patients developing new onset hyponatremia or new onset hypernatremia according to treatment assignment are shown in *Table 1*. Patients that developed hyponatremia more often had diabetes, chronic obstructive pulmonary disease, higher heart rate, lower baseline sodium and lower left ventricular ejection fraction in both the eplerenone group and placebo group. Patients that developed hypernatremia less often had diabetes, more often hypertension, had a lower heart rate, less symptomatic disease, more often higher baseline sodium and potassium levels, higher left ventricular ejection fraction and were less often treated with ACEi/ARBs in both the eplerenone and placebo group.

The proportion of patients developing new onset hyponatremia and hypernatremia is reflected in *figure 1*. In the eplerenone group, 11.3% of patients had one episode of new-onset hyponatremia and 3.4% of patients had ≥2 episodes (range 0-6 episodes). While 9.2% of the patients in the placebo group had one episode of new-onset hyponatremia and 2.3% of patients had ≥2 episodes (range 0-4 episodes). This illustrates that a larger proportion of patients receiving eplerenone developed new onset hyponatremia (p=0.0001), and a smaller proportion of patients receiving eplerenone developed new onset hypernatremia in comparison to placebo (p=0.0003). The proportion of patients with extreme sodium values (sodium < 130 mmol/l and sodium > 150 mmol/l) was low and did not differ according to the treatment assignment (see supplemental figure 1).

Sodium changes over time and predictors of sodium alterations

Figure 2 illustrates the absolute sodium values (panel A) and change in sodium values (panel B) at scheduled study follow-ups. At baseline, sodium was similar in the eplerenone group vs the placebo group (139.4±4.18 mmol/L vs. 139.5±4.53mmol/L). At first laboratory follow-up, which occurred 4 weeks after treatment assignment, serum sodium was significantly lower in patients assigned to eplerenone ($p<0.0001$) vs placebo. During follow-up, sodium remained relatively stable and did not decrease further (slope of curves in figure 2 [=sodium time*treatment interaction, $p=0.524$]). *Supplementary table 2* lists the independent predictors for the development of new onset hypo- or hypernatremia, illustrating that eplerenone assignment is associated with higher odds for new onset hyponatremia (OR=1.22; CI=1.03-1.44) and lower odds for new onset hypernatremia (OR=0.81; CI=0.72-0.92).

Sodium alterations and clinical outcome

Figure 3 illustrates the relation between the time-updated serum sodium levels and the different primary and secondary endpoints of the trial and the exploratory tertiary endpoints. For all endpoints (except CV-mortality $p=0.05$ instead of $p<0.05$) the association between the time-updated serum sodium levels and the outcome endpoint are different in the eplerenone group versus the placebo group, indicating that eplerenone significantly alters the relation between sodium levels and clinical outcome. More specifically, panel A and D (CV Mortality/CV Hospitalization and All Mortality/All Hospitalization) demonstrate that hyponatremia in subjects receiving eplerenone is not associated with an increased risk for the specific endpoint, while hyponatremia in patients treated with placebo is associated with an increased risk. For the remaining endpoints (panel B, E and F), hyponatremia remained associated with an increased risk for both the patients treated with placebo or eplerenone. Hyponatremia conveyed the largest risk for the endpoint HFH as illustrated by the largest hazard ratio. Hypernatremia was not associated with an increased risk for adverse outcome if patients were treated with eplerenone, while this was associated with an increased risk for all endpoints if patients were treated with placebo.

Sodium and the eplerenone treatment effect

Over the entire range of baseline sodium values, eplerenone was equally effective and baseline sodium did not modify the treatment effect of eplerenone (P for interaction >0.05 for all endpoints) (*table 2*). *Figure 4* represents the relation between the time updated serum sodium values (according to treatment assignment) and the risk of all different outcome endpoints after covariate adjustments. The risk is expressed as hazard ratio with corresponding confidence interval, and visualized using B-splines. *Figure 4* illustrates that the development of new onset hyponatremia was not associated with a reduction of the treatment effect of eplerenone, as indicated by all HR being below 1 (and sodium being expressed on a continuous scale). *Table 2* illustrates the hazard ratio for sodium expressed categorically (hyponatremia, normal sodium range and hypernatremia) similarly showing that development of post baseline hyponatremia was not associated with a reduction in the treatment effect of eplerenone as suggested by the directionality of the hazard ratios (all below 1).

Discussion

Our analysis of the EPHESUS trial offers novel and important information regarding the relation between MRA use and serum sodium in patients with an acute myocardial infarction complicated with systolic dysfunction. The main findings are reflected in *figure 5* and can be summarized as follows; **(1)** the use of eplerenone results in a lower serum sodium in comparison to placebo, which results in a higher proportion of patients developing hyponatremia and a lower proportion of patients developing hypernatremia during study follow-up. **(2)** Overall hyponatremia but not hypernatremia is associated with adverse outcome, **(3)** Eplerenone is effective in reducing mortality and morbidity irrespective of the baseline sodium. **(4)** Development of new-onset hyponatremia under eplerenone therapy does not diminish the beneficial treatment effect of eplerenone.

Hyponatremia frequently occurs in around 10-20% of patients with a myocardial infarction or heart failure (as we observed in the present study) and has long been recognized to confer an increased risk for adverse outcome.(1-6, 19, 20). Indeed this is also illustrated in supplemental table 1 showing that patient with baseline hyponatremia had more advanced disease, however our manuscript focusses on new onset hyponatremia and the relationship with MRA prescription. From a pathophysiologic

perspective, the hemodynamic and neurohormonal alterations that occur in the setting of a myocardial infarction or in the setting of heart failure predispose this patient population to develop hyponatremia.(21, 22) Both hemodynamic and neurohormonal alterations result in diminished distal nephron tubular flow.(23) While, neurohormones (renin and angiotensin II) result in non-osmotic release of arginine vasopressin (AVP).(24) Both low tubular flow and high levels of AVP predispose the distal nephron to the development of hyponatremia (see *figure 5*). Indeed serum sodium levels are fine-tuned in the distal nephron as direct micro-puncture studies have illustrated that tubular ultra-filtrate has a similar osmolality at the level of the macula densa in states of diuresis or anti-diuresis.(25)

Distal nephron sodium uptake by eNAC mitigates hyponatremia because free water is being reabsorbed in conjunction with sodium.(14) Not surprisingly, blocking this eNAC sodium uptake via MRAs results in heightened vulnerability to develop hyponatremia because free water is reabsorbed while sodium is being excreted.(26-28) Indeed, clinical practice guidelines on the use of diuretics in heart failure acknowledge that in the setting of acute heart failure that MRA use can worsen hyponatremia.(29) Yet , both in the setting of an acute myocardial infarction with a LVEF<40% as in the setting of HFrEF with symptoms despite optimal treatment with ACE-I/ARB and beta-blocker, MRAs carry a IA-guideline recommendation.(15, 16)

To the best of our knowledge, no study has evaluated the prognostic impact of potential serum sodium changes in relation to MRA in the setting of myocardial infarction complicated with systolic dysfunction. We show that the use of eplerenone is independently associated with the development of hyponatremia and patients treated with eplerenone have a small but statistically significant lower sodium throughout the study follow-up. Furthermore, we show in our cohort of patients with a myocardial infarction and systolic dysfunction that the presence of hyponatremia but not hypernatremia is associated with a high risk of adverse outcome for the primary, secondary and tertiary endpoints, with perhaps the strongest association between hyponatremia and the endpoint of HFH. It has indeed been well recognized that there is an inverse relation between neurohormonal activation and serum sodium, with a hyperreninemic state being associated with hyponatremia,(24, 30) which might explain why patients with hyponatremia are so vulnerable for developing heart failure

necessitating hospital admissions. Our data however is very reassuring from a clinical perspective. Indeed, despite the fact that eplerenone can reduce serum sodium levels, eplerenone works equally well in patients with a low baseline sodium. Therefore, Physicians should not refrain from prescribing eplerenone to eligible patients because of a low baseline sodium. In concordance with our data, a previous sub-analysis of the TRACE-trial (Trandolapril Cardiac Evaluation Study), baseline sodium did also not influence the treatment benefit of trandolapril in patients with an acute myocardial infarction complicated with systolic dysfunction.(5) Nevertheless, treatment with trandolapril did not result in a higher risk for developing hyponatremia during study follow-up, which was the case for eplerenone in our study.

We also assessed if patients who develop new onset hyponatremia following initiation of eplerenone could have had a lower treatment benefit. Reassuringly, the data indicates that patients who develop new onset hyponatremia have at least a similar treatment benefit of eplerenone. Although the p-values for interaction for the endpoints all-cause mortality, CV-mortality, and the composite of all-cause hospitalization and all-cause mortality suggest that patients with hyponatremia might have a bigger treatment benefit, this analysis should be interpreted with caution. This is because interaction tests between a treatment and a covariate measured after randomization can give a biased assessment of the treatment effect (because the measured covariate is also influenced by the treatment effect). Nevertheless, the directionality of the hazard ratios does indicate that new onset hyponatremia in the setting of eplerenone use is not associated with a reduction of the treatment effect. This is in analogy with several other observations in cardiology, such as a slight increase in potassium after initiation of spironolactone or an increase in creatinine after initiation of an ACE-I does not result in a loss of benefit from these drugs.(31-34) Interestingly, it is increasingly recognized that high sodium levels can also activate the mineralocorticoid receptor in a none aldosterone dependent way. This observation perhaps also explains why lower serum sodium levels in combination with eplerenone use conveyed the biggest treatment benefit.(35) Collectively this underscores the importance of eplerenone drug continuation even in the setting of baseline or development of hyponatremia.

Furthermore, our data also illustrates that perhaps in contrast to general belief hypernatremia is relatively common in heart failure occurring in 22% of patients using eplerenone and in 26% of

patients on placebo. However in comparison to available literature, the prevalence of hypernatremia is not much different. (2, 36) Furthermore, our data illustrates that hypernatremia in comparison to hyponatremia is not associated with adverse clinical outcome.

Limitations

Several limitations should be noted in the present analysis. This is a post-hoc analysis of a randomized controlled trial, therefore these findings should be regarded as hypothesis generating. Second, on the absolute sodium values the effect of eplerenone is relatively small, but the change is very consistent in the overall population. Third, analysis between post randomization covariates and treatment can result in a biased assessment of a treatment effect. Fourth, in clinical practice, community physicians may respond to hyponatremia either by sodium supplementation of fluid restriction. However, there was no information on this practice in the current dataset and our analyses cannot address the impact of such practices on responsiveness to eplerenone.

Conclusion

In patients with left ventricular systolic dysfunction after myocardial infarction, treatment with eplerenone resulted in a lower serum sodium over time and a higher proportion of patients developing new onset hyponatremia. Overall hyponatremia but not hypernatremia is associated with adverse outcome. However, over the entire baseline serum sodium spectrum, treatment with eplerenone improves clinical outcome. New-onset hyponatremia after eplerenone initiation is not associated with a diminution of the eplerenone treatment effect.

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Data sharing policy

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer

Table 1: Characteristics of patients with hyponatremia or hypernatremia at post-baseline visit according to treatment assignment

Parameter	Eplerenone (N= 2797)						Placebo (N= 2799)					
	No hypo-natremia (N=2386)	Hypo-natremia (N=411)	p-value	No hyper-natremia (N=2284)	Hyper-natremia (N=642)	p-value	No hypo-natremia N=2477)	Hypo-natremia (N=322)	p-value	No hyper-natremia (N=2136)	Hyper-natremia (N=757)	p-value
Demographics and comorbidities												
Age, years	63.5±11.3	64.5±11.6	0.08	63.6±11.5	63.2±10.8	0.35	63.7±11.7	63.8±11.9	0.90	64.1±12.1	63.5±10.8	0.22
Male gender	1711 (72%)	292 (71%)	0.78	1665 (73%)	458 (71%)	0.43	1777 (72%)	222 (69%)	0.30	2136 (70%)	549 (73%)	0.26
Diabetes	694 (29%)	151 (37%)	0.003	789 (35%)	159 (25%)	<0.0001	749 (30%)	117 (36%)	0.047	739 (35%)	203 (27%)	0.0001
Hypertension	1412 (59%)	250 (61%)	0.59	1301 (57%)	420 (65%)	0.0001	1506 (61%)	204 (63%)	0.38	1236 (58%)	504 (67%)	<0.001
Atrial fibrillation	294 (12%)	57 (14%)	0.25	283 (12%)	92 (14%)	0.09	307 (12%)	43 (13%)	0.23	271 (14%)	97 (13%)	0.86
COPD	208 (9%)	45 (11%)	0.009	202 (9%)	62 (10%)	0.16	227 (9%)	36 (11%)	0.037	212 (10%)	70 (9%)	0.11
Previous MI	642 (27%)	122 (30%)	0.24	638 (28%)	168 (26%)	0.38	629 (25%)	98 (30%)	0.052	552 (26%)	202 (27%)	0.65
PAD	272 (11%)	62 (15%)	0.040	272 (12%)	81 (13%)	0.82	296 (12%)	48 (15%)	0.29	284 (13%)	92 (12%)	0.63
Physical features												
SBP, mmHg	119±17	119±16	0.62	118±17	121±16	0.003	119±16	120±17	0.34	119±17	120±16	0.022
DBP, mmHg	73±11	72±11	0.62	72±11	74±10	0.003	72±10	72±10	0.34	71±11	73±10	0.022
Heart rate, bpm	74±12	76±13	0.006	75±12	74±12	0.053	74±11	75±12	0.035	75±12	73±16	0.0002
Killip class I-II	1950 (82%)	319 (79%)	0.12	1820 (80%)	526 (82%)	0.014	2015 (82%)	250 (79%)	0.48	1691 (80 (%)	624 (83%)	0.0003

Killip clas II-III	427 (18%)	84 (21%)	0.12	445 (20%)	116 (18%)	0.014	449 (18%)	66 (21%)	0.48	429 (20%)	128 (17%)	0.0003
Laboratory features												
Hemoglobin, g/dl	13.3±1.7	13.2±1.9	0.16	13.3±1.7	13.3±1.7	0.81	13.4±1.7	13.3±1.9	0.30	13.3±1.8	13.5±1.7	0.013
Sodium, mmol/L	140.6±3.9	139.2±3.5	<0.001	138.5±3.5	140.2±3.6	<0.0001	140±3.4	139±3.5	<0.001	138.3±3.5	140.5±3.2	<0.0001
Potassium, mmol/L	4.3±0.4	4.3±0.5	0.52	4.3±0.5	4.3±0.4	0.0005	4.3±0.4	4.3±0.6	0.67	4.2±0.5	4.3±0.4	<0.0001
eGFR< 60 ml/min/1,73m^2	948 (40%)	176 (43%)	0.21	909 (40%)	265 (41%)	0.53	983 (40%)	115 (36%)	0.17	843 (40%)	299 (40%)	0.99
Heart failure features												
LVEF, %	34±6	33±6	0.0013	33±6	34±6	0.0002	34±6	33±7	0.026	33±6	34±6	<0.0001
Previous HFH	171 (8%)	42 (7%)	0.42	171 (8%)	42 (7%)	0.42	168 (8%)	81 (7%)	0.31	168 (8%)	51 (7%)	0.63
ACEi/ARB	2051 (86%)	360 (88%)	0.38	2012 (88%)	530 (83%)	0.0002	2162 (87%)	280 (87%)	0.87	1898 (89%)	640 (85%)	0.002
Beta-blocker	1837 (77%)	273 (66%)	<0.0001	1725 (76%)	476 (74%)	0.47	1900 (77%)	241 (75%)	0.46	1611 (75%)	584 (77%)	0.34
Loop diuretic	1357 (57%)	262 (64%)	0.008	1362 (60%)	364 (57%)	0.18	1450 (59%)	191 (59%)	0.52	1304 (61%)	423 (56%)	0.013
Thiazide use	197 (8%)	41 (10%)	0.25	191 (8%)	62 (10%)	0.062	184 (7%)	23 (7%)	0.85	156 (7%)	62 (8%)	0.42

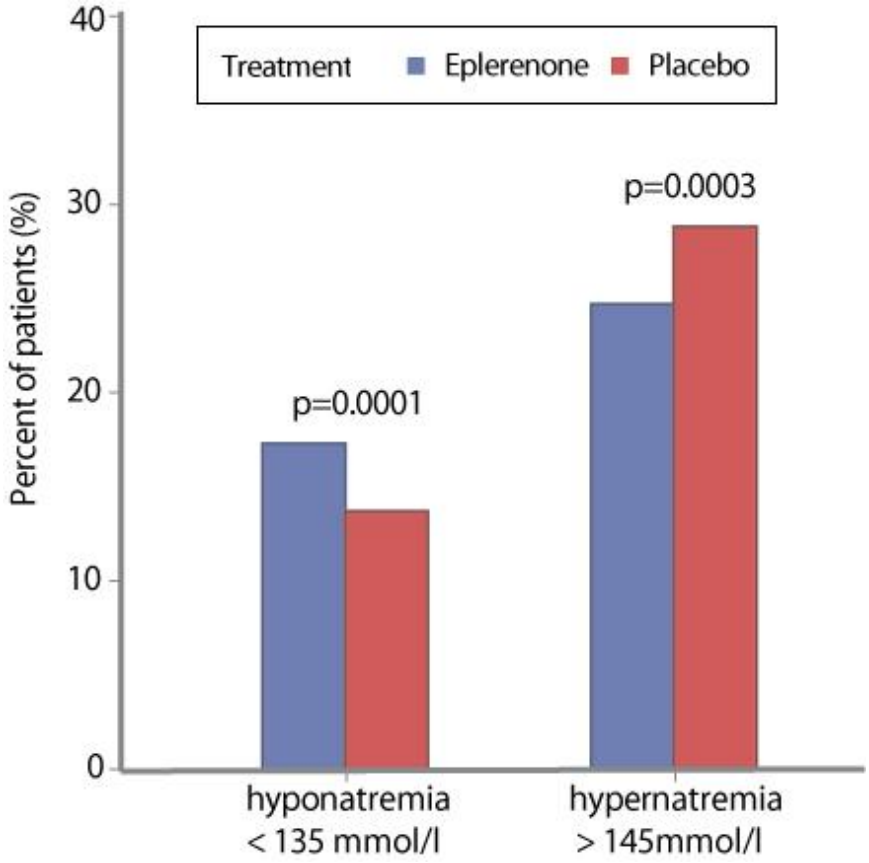
Abbreviations: ACEi= angiotensin converting enzyme inhibitors, ARB= angiotensin receptor blokkers, Bpm= beats per minute, COPD= chronic obstructive pulmonary disease, DBP= diastolic blood pressure, eGFR= estimated glomerular filtration rate, PAD= peripheral artery disease, MI= myocardial infarction, SBP= systolic blood pressure.

Table 2: Treatment interaction of eplerenone effect in hyponatremia versus normal sodium range.

Endpoint	Baseline sodium		Follow-up sodium	
	HR (95% CI)	p-value for interaction	HR (95% CI)	p-value for interaction
CV-mortality and CV-hospitalizatio	HypoNa: 0.96 (0.72 -1.30)	0.25	HypoNa: 067 (0.47 -1.03)	0.035
	Normal Na: 0.91 (0.81 -1.02)		Normal Na: 0.92 (0.82 -1.03)	
	HyperNa: 1.03 (0.68 -1.58)		HyperNa: 0.70 (0.50 -0.98)	
All-cause mortality	HypoNa: 1.27 (0.84-1.91)	0.79	HypoNa: 0.69 (0.47-1.03)	0.08
	Normal Na: 0.94 (79 -1.12)		Normal Na: 0.97 (0.82 -1.14)	
	HyperNa: 0.71 (0.36 -1.40)		HyperNa: 0.52 (0.31 -0.87)	
CV-mortality	HypoNa: 1.23 (0.80 – 1.91)	0.41	HypoNa: 0.64 (0.41 – 0.99)	0.024
	Normal Na: 0.95 (0.79 -1.15)		Normal Na: 0.98 (0.82 -1.17)	
	HyperNa: 0.72 (0.33 -1.60)		HyperNa: 0.51 (0.30 -0.87)	
All-cause mortality and all cause hospitalization	HypoNa: 1.04 (0.83 -1.30)	0.90	HypoNa: 0.66 (0.50 -0.85)	0.003
	Normal Na: 0.98 (0.91 -1.07)		Normal Na: 0.99 (0.92-1.07)	
	HyperNa: 0.98 (0.72 -1.34)		HyperNa: 0.78 (0.61 -0.99)	
HFH and CV-mortality	HypoNa: 0.95 (0.71 -1.23)	0.83	HypoNa: 0.74 (0.52 -1.05)	0.16
	Normal Na: 0.91 (0.80 -1.02)		Normal Na: 0.88 (0.78 -1.01)	
	HyperNa: 0.98 (0.72 -1.34)		HyperNa: 0.61 (0.41 -0.91)	
HFH	HypoNa: 0.78 (0.51 -1.19)	0.98	HypoNa: 0.92 (0.61 -1.40)	0.47
	Normal Na: 0.82 (0.69 -0.97)		Normal Na: 0.81 (0.69 -0.96)	
	HyperNa: 0.80 (0.42 -1.51)		HyperNa: 0.61 (0.36 -1.03)	

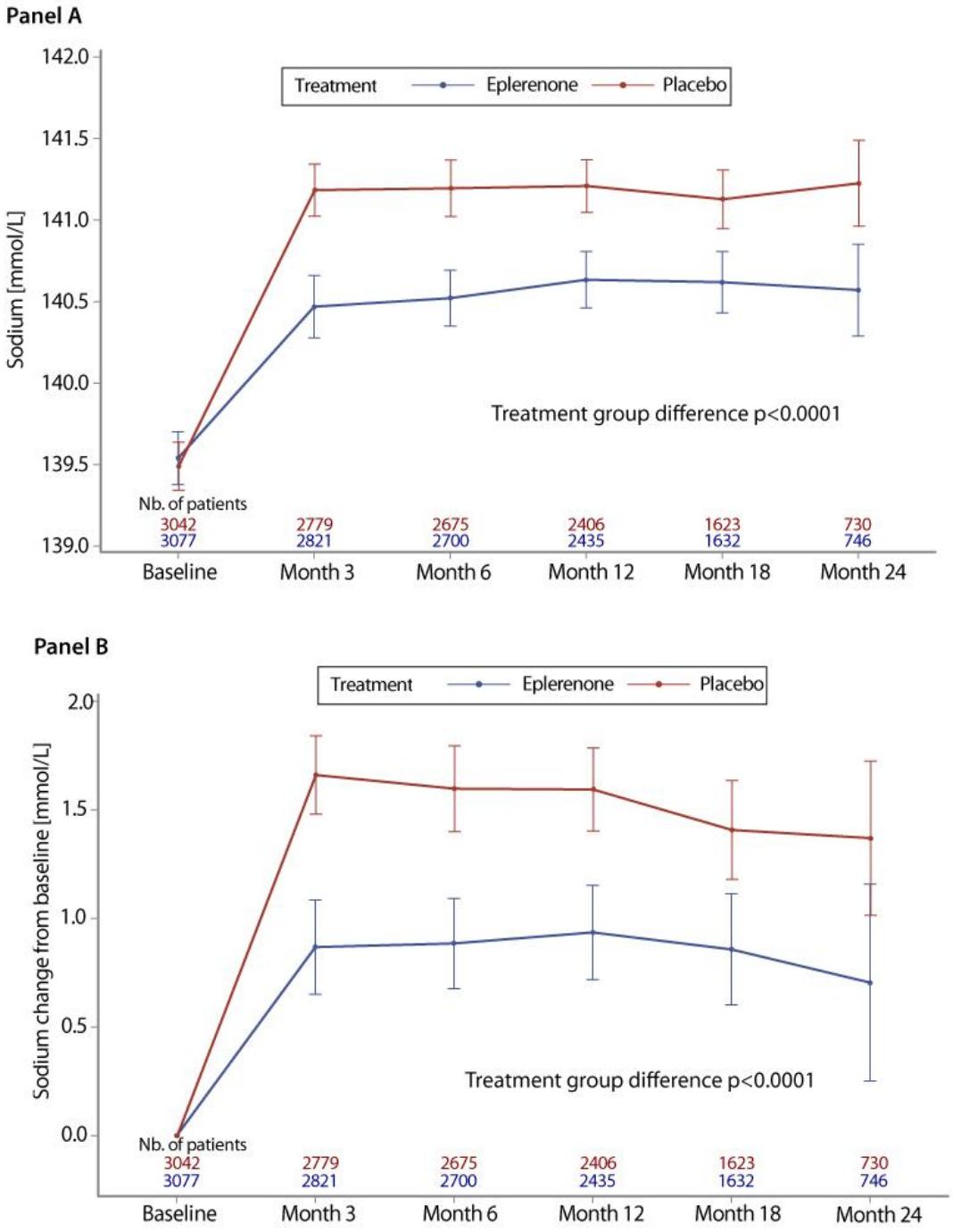
Explanation: the hazard ratios are the result of a multivariable model with covariate adjustment as describe in the statistical section. **Abbreviations:** CV= cardiovascular, HFH= heart failure hospitalization, HR= hazard ratio, Na= sodium.

Figure 1: Hypo- and hypernatremia at any postbaseline visit according to treatment assignment.



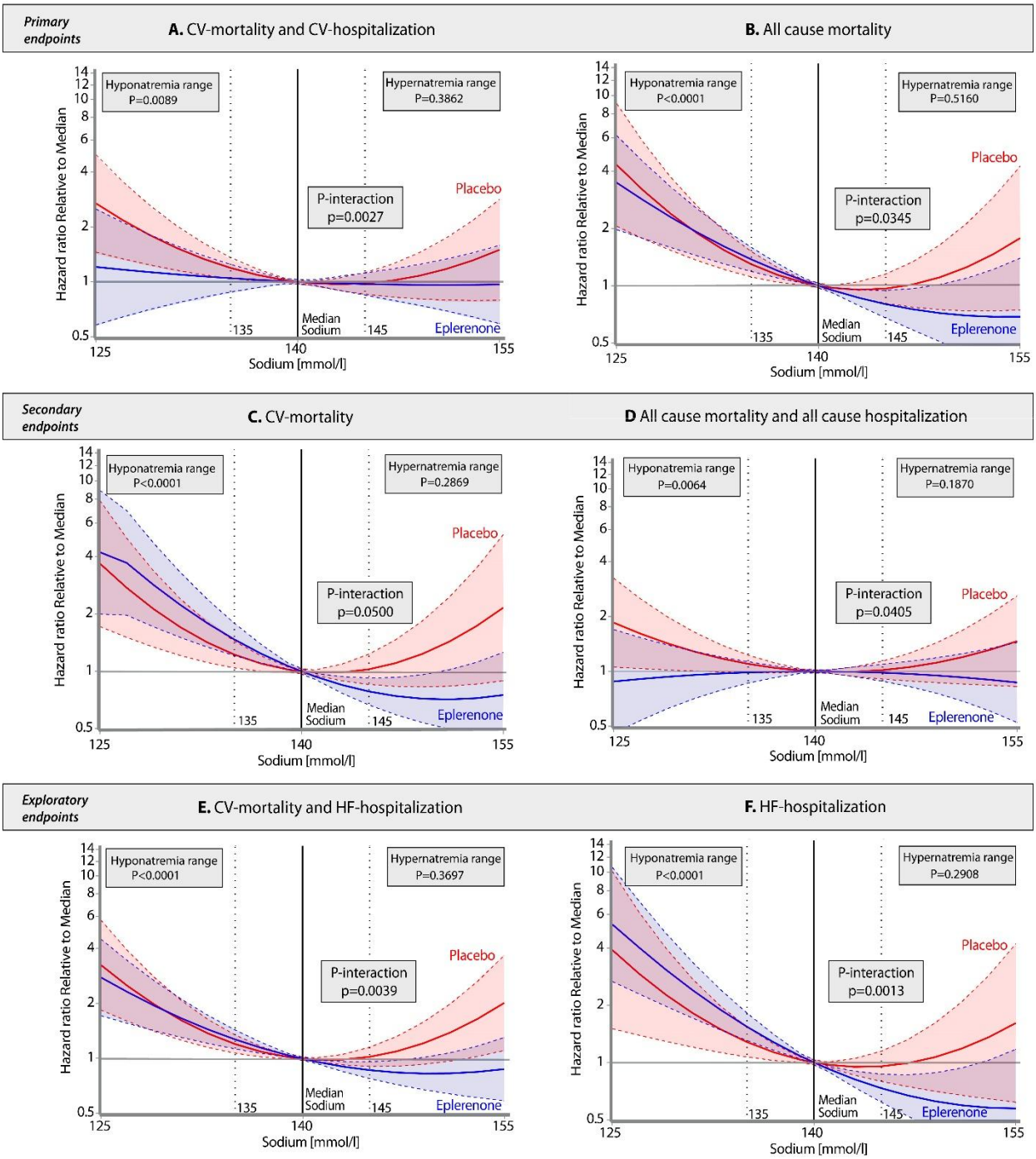
Explanation: classification according to post-baseline visit sodium values. P-values are based on the Fisher's exact test. Patients can contribute to both groups is a patients has both a hypo- and hypernatremia event during follow-up.

Figure 2: Sodium values over time according to treatment assignment



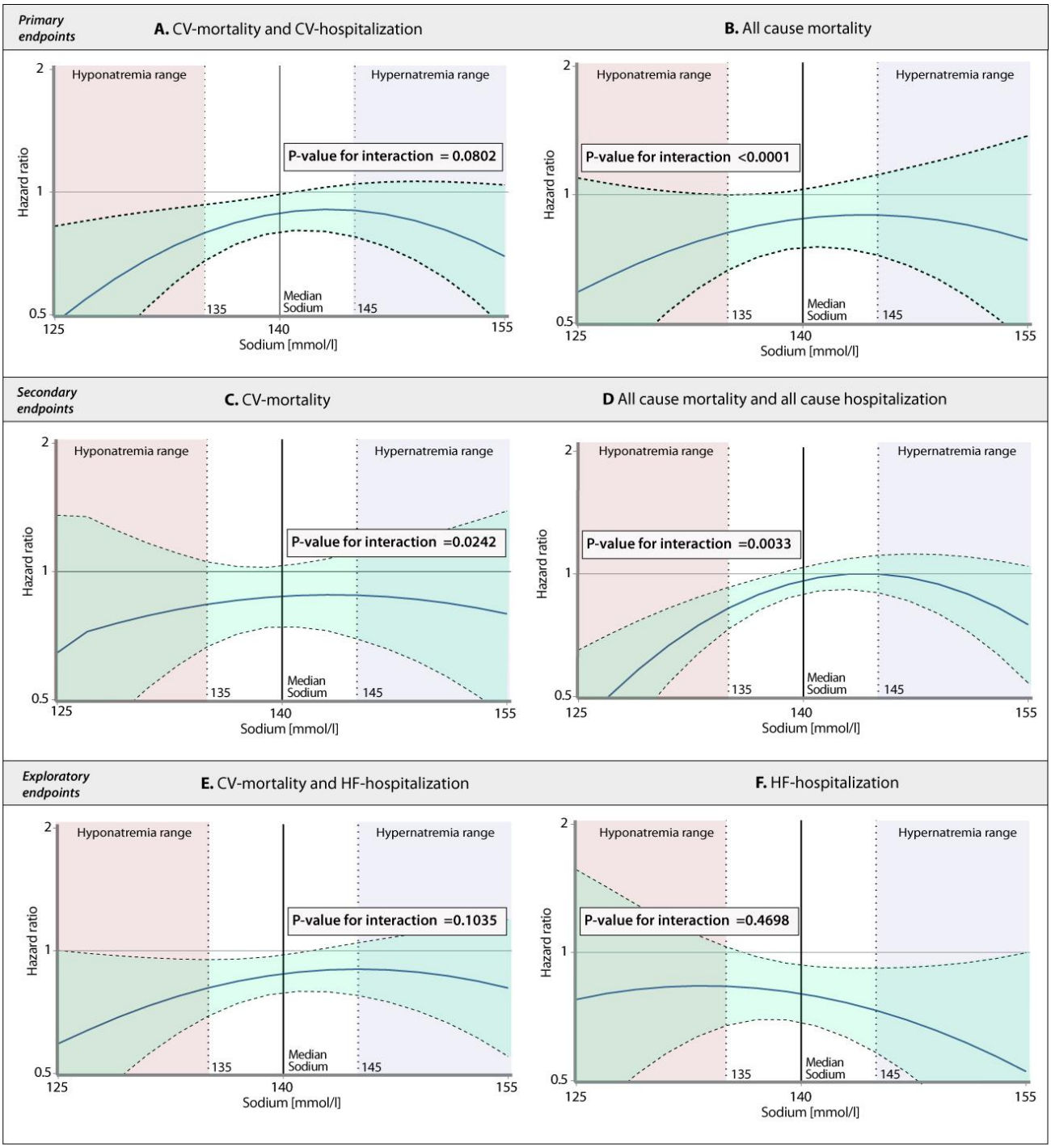
Explanation: longitudinal sodium values (panel A) and change from baseline in sodium (panel B). Values indicate means and 95% confidence interval. Numbers of patients at risk at every planned visit are reflected. P-value is the result of a general linear model with baseline sodium and treatment assignment as covariates.

Figure 3: Adjusted risk for different endpoints according to sodium level vs median sodium



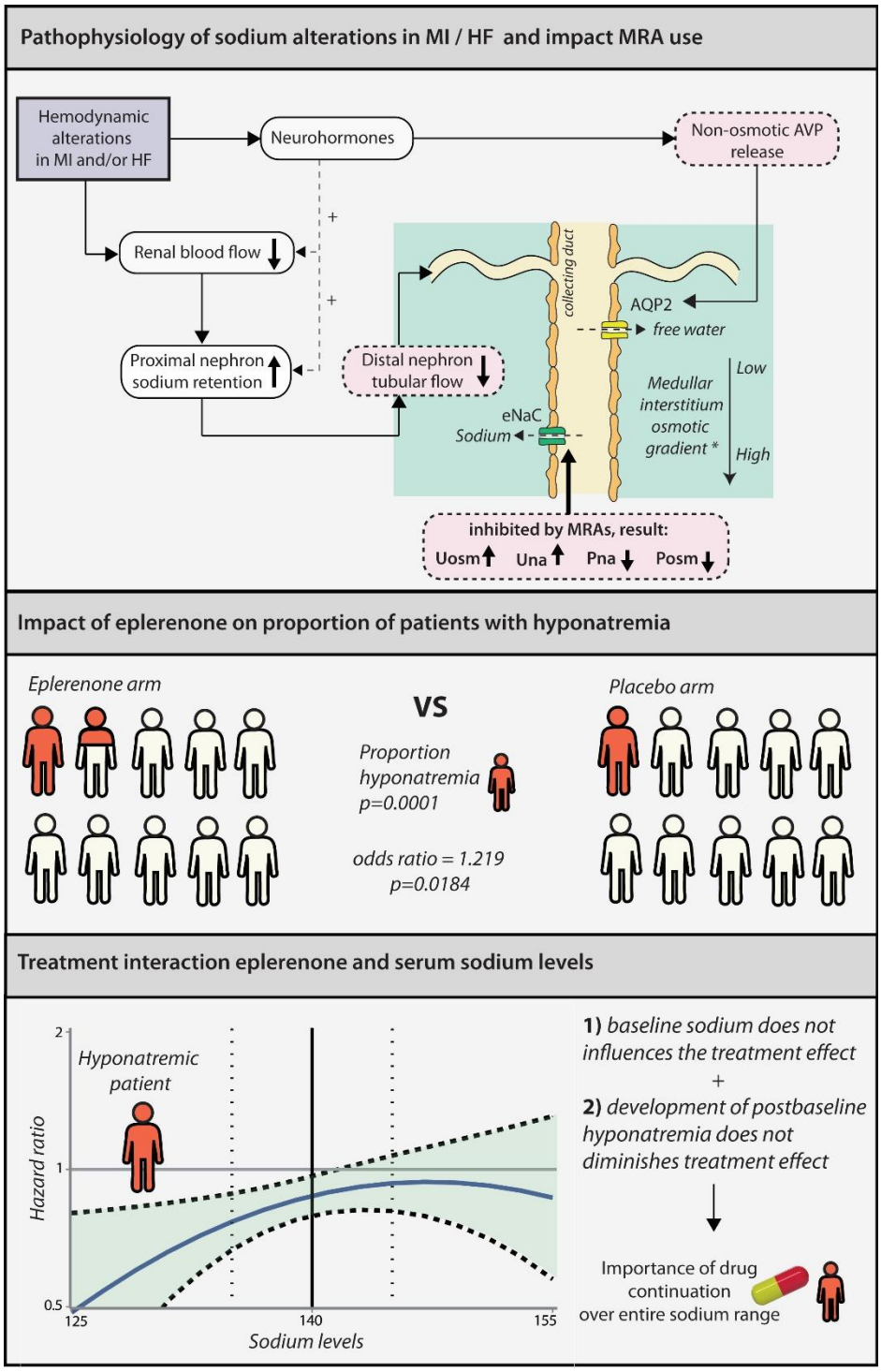
Explanation: Multiple panel figure of the hazard ratio and confidence interval of a specific sodium value on the sodium spline curve versus the median sodium value (reference of 140mmol/l). Models are adjusted for the covariates outlined in the statistical analysis section, with covariates reaching statistical significance entering the model. All models always include baseline sodium, spline effects of time varying sodium values and treatment assignment. Panel A and B are the primary endpoints of the EPHESUS trial, panel C and D the secondary endpoints of the EPHESUS trials and Panel E and F the exploratory endpoints for this analysis. Red areas indicate placebo treatment arm, while light blue areas indicate eplerenone treatment arm.

Figure 4: Eplerenone treatment effect according to serum sodium after randomization.



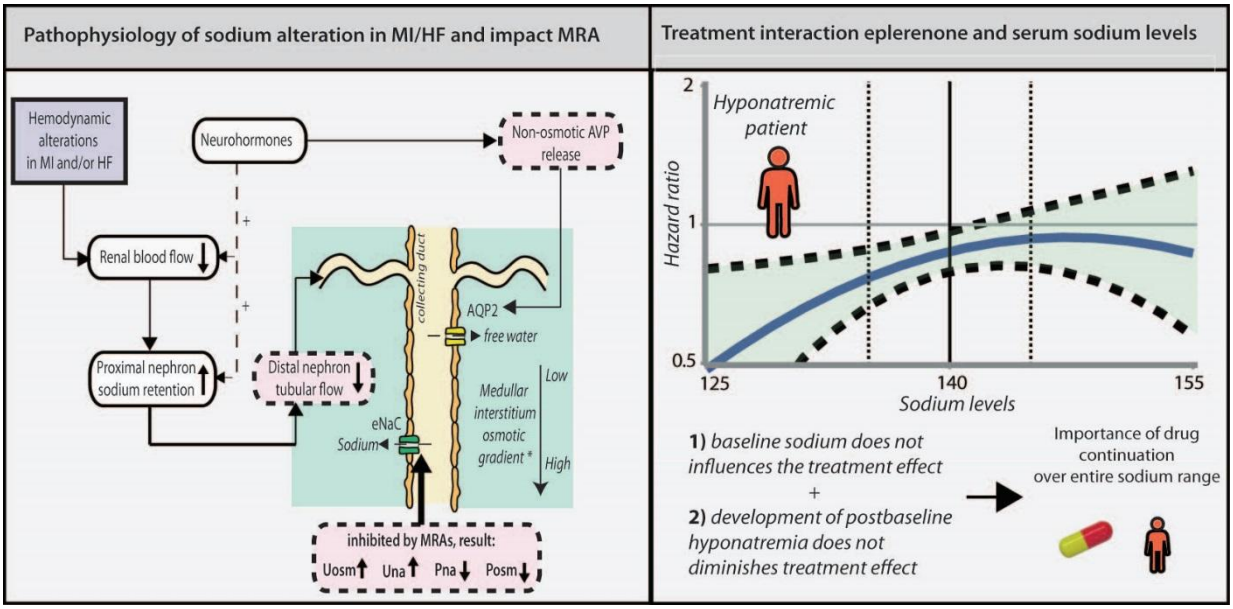
Explanation: Multiple panel figure of the hazard ratio and confidence interval for the risk for the endpoint at any given sodium value after randomization for eplerenone versus placebo. Models are adjusted for the covariates outlined in the statistical analysis section, with covariates reaching statistical significance entering the model. All models include baseline sodium, spline effects of time varying sodium values and treatment assignment and treatment sodium interaction. Reported p-value is the p-value for interaction of the treatment * sodium interaction, with sodium defined as categories (hyponatremia <135mmol/l, normal=135-145mmol/l and hypernatremia>145mmol/l). Panel A and B are the primary endpoints of the EPHESUS trial, panel C and D the secondary endpoints of the EPHESUS trials and Panel E and F the exploratory endpoints for this analysis. Light red areas indicate hyponatremia values, while light blue areas indicate hypernatremia values. The green area indicates the treatment effect.

Figure 5: Impact of eplerenone on sodium concentration and prognostic relevance



Explanation: panel A depicts the mechanisms of hyponatremia in heart failure and the worsening of by MRAs. Low tubular flow in the distal nephron and the permeability of the distal nephron to free water are the main determinants of free water uptake and thus plasma sodium levels. *= indicates that medullar interstial oncotic gradient drives free water uptake and is higher due to low renal blood flow (less washout by vasa-recta) and due to medullar urea retention driven by AVP. Panel B illustrates that eplerenone is an independent predictor for hyponatremia. However the treatment effect of eplerenone is the biggest in patients in the hyponatremic range as illustrated in panel C. **abbreviations:** AVP= arginine vasopressin, AQP2= aquaporine channel 2, eNaC= aldosterone sensitive epithelial Na-channel.

Visual abstract: Serum sodium and eplerenone use in patients with a myocardial infarction and left ventricular dysfunction or heart failure: insights from the EPHESUS trial



Supplemental table 1: Baseline characteristics of patients with versus without post-baseline sodium values.

Parameters	Patients with post baseline sodium (N= 6221)	Patients without post baseline sodium (N= 411)	p-value
Demographics and comorbidities			
Age, years	63.7±11.5	67.5±114	<0.0001
Male gender	4439 (71%)	275 (67%)	0.0542
Diabetes	1992 (32%)	150 (37%)	0.0170
Hypertension	3748 (60%)	259 (63%)	0.2661
Atrial fibrillation	542 (9%)	54 (13%)	0.0005
COPD	321 (5%)	29 (7%)	0.2059
Previous MI	1668 (27%)	135 (33%)	0.0077
PAD	460 (7%)	43 (11%)	0.0663
Physical features			
SBP, mmHg	119±16	117±17	0.0103
DBP, mmHg	72±11	71±12	0.1084
Heart rate, bpm	74±12	79±13	<0.0001
Killip class I-II	4990 (81%)	299 (73%)	<0.0001
Killip clas II-III	1191 (19%)	111 (27%)	
Laboratory features			
Hemoglobin, g/dl	13.4±1.7	13.0±1.7	0.0073
Sodium, mmol/L	139.5±4.1	138.1±4.5	<0.0001
Potassium, mmol/L	4.3±0.5	4.2±0.4	0.0599
eGFR< 60 ml/min/1,73m²	1239 (40%)	116 (58%)	<0.0001
Heart failure features			
LVEF, %	33±6	30±7	<0.0001
Previous HFH	463 (7%)	49 (12%)	0.0010
ACEi/ARB	5402 (87%)	349 (85%)	0.2667
Beta-blocker	4695 (76%)	266 (65%)	<0.0001
Loop diuretic	3384 (54%)	277 (67%)	<0.0001
Thiazide use	504 (8%)	36 (9%)	0.6369

Abbreviations: ACEi= angiotensin converting enzyme inhibitors, ARB= angiotensin receptor blokkers, Bpm= beats per minute, COPD= chronic obstructive pulmonary disease, DBP= diastolic blood pressure, eGFR= estimated glomerular filtration rate, PAD= peripheral artery disease, MI= myocardial infarction, SBP= systolic blood pressure.

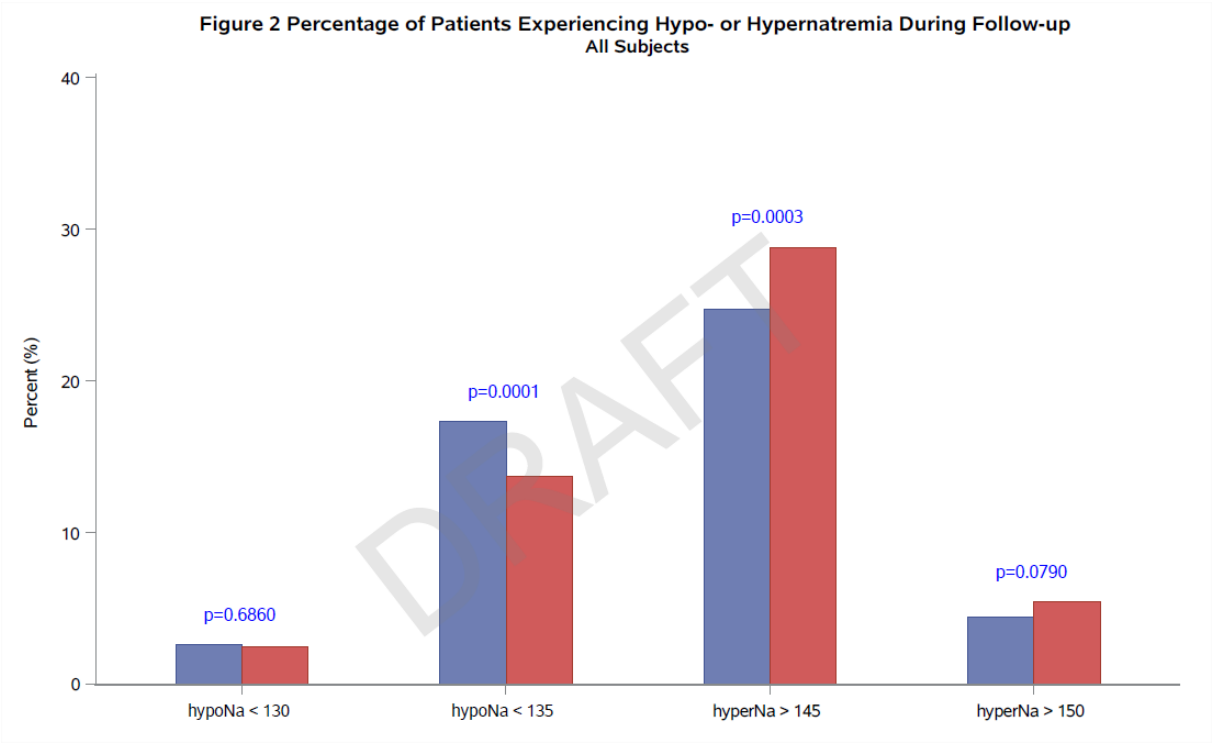
Supplemental table 2: Multivariable logistic models for independent predictors of hypo- and hypernatremia

Parameter	Hyponatremia			Hypernatremia		
	Odds	95% CI	p-value	Odds	95% CI	p-value
Baseline sodium [a]	0.977	0.958-0.997	0.0223	1.059	1.044-1.075	<0.0001
Reperfusion therapy	0.720	0.610-0.850	0.0001	0.681	0.601-0.771	<0.0001
PCI	0.718	0.588-0.877	0.0011	0.633	0.542-0.737	<0.0001
LVEF [b]	0.985	0.972-0.998	0.0226	1.030	1.018-1.041	<0.0001
Diabetes type II	1.241	1.044-1.475	0.0142	0.706	0.613-0.813	<0.0001
Hypertension	1.123	0.950-1.328	0.1731	1.397	1.229-1.589	<0.0001
Baseline potassium [c]	1.001	0.834-1.203	0.9874	1.397	1.214-1.606	<0.0001
Eplerenone assignment	1.219	1.034-1.437	0.0184	0.814	0.719-0.920	0.0010
Heart rate [d]	1.010	1.003-1.0016	0.0066	0.993	0.987-0.998	0.0073
Killip class II vs I	1.220	0.985-1.555	0.1074	1.385	1.155-1.660	0.0004
Killip class III vs I	1.277	0.949-1.719	0.1061	1.201	0.957-1.508	0.1134
Use of diuretics	1.111	0.939-1.315	0.2208	0.831	0.734-0.940	0.0034
Previous HFH	1.496	1.138-1.967	0.0039	0.869	0.678-1.112	0.2646
Systolic BP [e]	1.001	0.996-1.006	0.6444	1.006	1.002-1.009	0.0034
History of COPD	1.387	0.943-2.040	0.0968	1.408	1.052-1.884	0.0212
Previous MI	1.254	1.049-1.498	0.0128	0.990	0.861-1.139	0.8913
Thrombolysis	0.896	0.744-1.080	0.2483	0.855	0.743-0.984	0.0294
History of PAD	1.432	1.014-2.023	0.0413	1.086	0.816-1.444	0.5716
Hemoglobin [f]	0.971	0.926-1.018	0.2269	1.029	0.992-1.066	0.1246
Age [g]	1.005	0.998-1.012	0.1764	0.997	0.991-1.002	0.2377
History of AF	0.892	0.577-1.380	0.6088	0.983	0.720-1.344	0.9158
BMI [h]	0.990	0.972-1.008	0.2850	1.001	0.988-1.015	0.8919
Gender (M vs F)	0.930	0.778-1.112	0.4250	1.019	0.889-1.168	0.7828
CABG	0.790	0.337-1.852	0.5873	0.846	0.457-1.567	0.5958
eGFR [i]	1.000	0.996-1.004	0.9162	1.001	0.998-1.004	0.5757

Explanation: results of multivariable logistic model with categories hyponatremia and hypernatremia being compared to the reference of normal sodium (135-145 mmol/l). Categorization into hyponatremia and hypernatremia category is based on post-baseline sodium values as defined in the methods section. Patients with hyponatremia at baseline that remained in hyponatremia post-baseline were included in the reference category as they did not develop new onset hyponatremia. Superscripts denote a: per mmol/l sodium increase, b:per % increase in LVEF, c:per mmol/l K increase, d:per beat per minute increase, e: per mmHg increase, f: per g/dl increase, g: per year increase, h: per kg/m² increase, i: per mg/dl/1,73m² increase.

Abbreviations: AF= atrial fibrillation, BP= blood pressure, BMI= body mass index, CABG= coronary artery bypass grafting, COPD= chronic obstructive pulmonary disease, eGFR= estimated glomerular filtration rate, F= female, HFH= heart failure hospitalization, LVEF= left ventricular ejection fraction, M= male, MI= myocardial infarction, PCI= percutaneous coronary intervention, PAD= peripheral artery disease.

Supplemental figure 1



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