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RESEARCH ARTICLE

Hyponatraemia and changes in natraemia during hospitalization for acute heart failure and associations with in-hospital and long-term outcomes – from the ESC-HFA EORP Heart Failure Long-Term Registry

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Aims To comprehensively assess hyponatraemia in acute heart failure (AHF) regarding prevalence, associations, hospital course, and post-discharge outcomes.

Methods and results Of 8298 patients in the European Society of Cardiology Heart Failure Long-Term Registry hospitalized for AHF with any ejection fraction, 20% presented with hyponatraemia (serum sodium <135 mmol/L). Independent predictors included lower systolic blood pressure, estimated glomerular filtration rate (eGFR) and haemoglobin, along with diabetes, hepatic disease, use of thiazide diuretics, mineralocorticoid receptor antagonists, digoxin, higher doses of loop diuretics, and non-use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers. In-hospital death occurred in 3.3%. The prevalence of hyponatraemia and in-hospital mortality with

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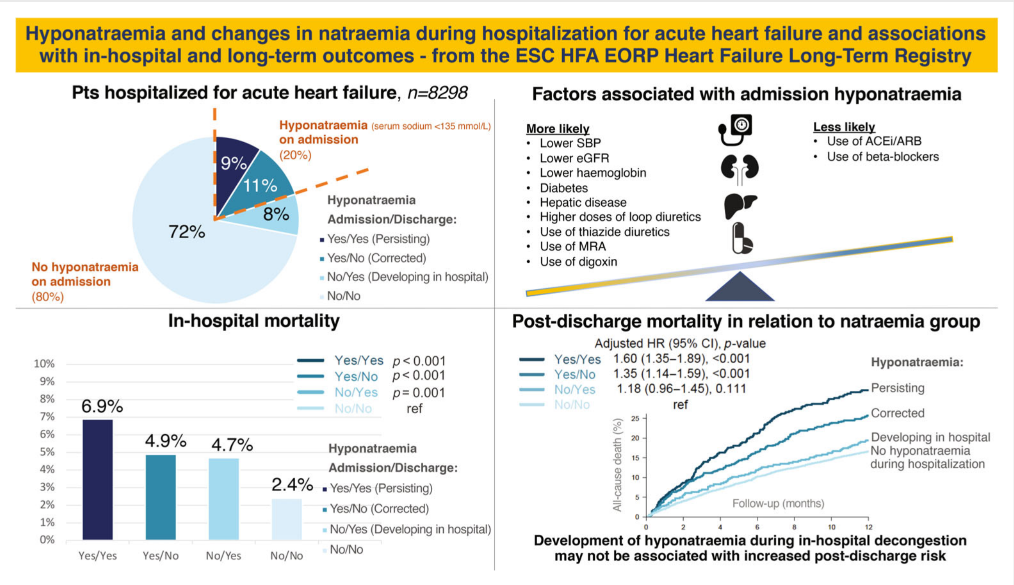
different combinations were: 9% hyponatraemia both at admission and discharge (hyponatraemia Yes/Yes, in-hospital mortality 6.9%), 11% Yes/No (in-hospital mortality 4.9%), 8% No/Yes (in-hospital mortality 4.7%), and 72% No/No (in-hospital mortality 2.4%). Correction of hyponatraemia was associated with improvement in eGFR. In-hospital development of hyponatraemia was associated with greater diuretic use and worsening eGFR but also more effective decongestion. Among hospital survivors, 12-month mortality was 19% and adjusted hazard ratios (95% confidence intervals) were for hyponatraemia Yes/Yes 1.60 (1.35–1.89), Yes/No 1.35 (1.14–1.59), and No/Yes 1.18 (0.96–1.45). For death or heart failure hospitalization they were 1.38 (1.21–1.58), 1.17 (1.02–1.33), and 1.09 (0.93–1.27), respectively.

Conclusion Among patients with AHF, 20% had hyponatraemia at admission, which was associated with more advanced heart failure and normalized in half of patients during hospitalization. Admission hyponatraemia (possibly dilutional), especially if it did not resolve, was associated with worse in-hospital and post-discharge outcomes. Hyponatraemia developing during hospitalization (possibly depletional) was associated with lower risk.

Graphical Abstract



In patients with acute heart failure, 20% had hyponatreamia at hospital admission, which was associated with more advanced heart failure and normalized in half of patients during hospitalization. Admission hyponatreamia (possibly dilutional), especially persisting during hospitalization, was associated with worse in-hospital and post-dicharge prognosis. Hyponatraemia developing during hospitalization (possibly depletional) was associated with lower risk. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.

Keywords Acute heart failure • Worsening heart failure • Hyponatraemia • Sodium • Prognosis • Congestion

Introduction

Hyponatraemia is the most common electrolyte imbalance, with a prevalence in hospitalized heart failure (HF) patients reported at 10–30%.[1–10] In acute HF (AHF), hyponatraemia is mainly dilutional and results from venous congestion and poor perfusion, and elevated vasopressin concentrations leading to free water retention.[5] It reflects neurohormonalactivation, fluid retention, and congestion, and is associated with worse in-hospital and long-term prognosis.[1–8] Up to a half of HF patients suffer from frequent thirst, which results from neurohormonal activation and HF treatment, and may lead to increased fluid intake.[11,12] Limited data are available regarding risk markers and risk factors for hyponatraemia at AHF hospitalization and the associations between changes of sodium concentration during hospitalization and post-discharge prognosis in HF. Compared to persistent hyponatraemia, corrected hyponatraemia may be associated with lower risk of death and HF rehospitalization.[3,10] Still, although the vasopressin receptor blocker tolvaptan appears effective in correcting hyponatraemia and reducing congestion, it had no effect on long-term mortality or HF-related morbidity in AHF.[5,6,9] While aggressive diuresis in AHF may also lead to depletional hyponatraemia due to sodium losses, its effects on long-term outcomes remain unknown.[13,14]

The aim of this analysis was to assess hyponatraemia and serum sodium changes during hospitalization for AHF irrespective of ejection fraction (EF) with regard to prevalence, predictors, in-hospital clinical course and mortality, and post-discharge outcomes.

Methods

Study design and patient selection

The European Society of Cardiology-Heart Failure Association (ESC-HFA) EURObservational Research Programme (EORP) HF Long-Term Registry was an international, multicentre, prospective registry of adult HF patients, conducted between 2011 and 2018 in cardiology centres from 33 ESC member countries (online supplementary *Appendix S1*). The registry included both outpatients with chronic HF and patients hospitalized for AHF. AHF was defined as HF symptoms and signs requiring intravenous HF treatment, including inotropes, intravenous diuretics and/or intravenous vasodilators.[15–17] To ensure representativeness of the HF population, centres across a varied range of facilities were included in proportion to the size of the population of the participating countries.[16] For hospitalized patients, data were captured both at admission and discharge, allowing assessment of in-hospital course and mortality, and at 1-year follow-up, allowing capture of post-discharge cause-specific hospitalization and mortality. Detailed methodology of the ESC-HFA EORP HF Long-Term Registry has been previously published.[15–17] It was approved by local ethics committees according to the regulations of each participating country. All patients gave written, informed consent.

The current study was a retrospective analysis of data from the ESC-HFA EORP HF Long-Term Registry, and included patients hospitalized for AHF for whom data on sodium concentration both on admission and at discharge were available. In the registry, discharge values indicated the last measurements performed during hospitalization and were available also for patients who died during hospitalization. Hyponatraemia was defined as serum sodium concentration <135 mmol/L.

Patients were divided into four groups:

(1) hyponatraemia both on admission and at discharge (or at last measurement in case of in-hospital death) (hyponatraemia Yes/Yes),
(2) hyponatraemia on admission but not at discharge (Yes/No),
(3) no hyponatraemia on admission but with hyponatraemia at discharge (No/Yes),
(4) hyponatraemia neither on admission nor at discharge (No/No) – reference group for statistical comparisons.

The four natraemia groups were then assessed with regard to baseline characteristics, predictors of hyponatraemia at admission, in-hospital clinical course, predictors of in-hospital natraemia changes, and in-hospital mortality. Next, for patients who survived to hospital discharge, we evaluated the association between the four natraemia groups, that is, capturing changes in serum sodium during hospitalization, and post-discharge outcomes. The primary outcome was a composite of all-cause death and first HF rehospitalization. The secondary endpoint was all-cause death. Tertiary endpoints included cardiovascular death, HF death, all-cause rehospitalizations, cardiovascular rehospitalizations and HF rehospitalizations at follow-up.

Post-discharge outcome analyses were repeated in important subgroups such as according to EF category (HF with reduced, mildly reduced, and preserved EF) or to kidney function (estimated glomerular filtration rate [eGFR] above or below 60 ml/min/1.73 m^2).

Statistical analysis

Baseline characteristics are defined as those at the time of hospital admission. Categorical data are reported as percentages and compared with the χ^2 test. Continuous variables are presented as median and interquartile range (IQR) or as mean ± standard deviation, as appropriate, and compared with Kruskal–Wallis tests.

To identify predictors of hyponatraemia at hospital admission, and predictors of correction of hyponatraemia during hospitalization, we performed multivariable logistic regression analyses including variables shown in *Tables 1* and *2*. Apart from those variables, the cause of HF decompensation was also included in both multivariable analyses. For predictors of correction, percent increase in eGFR from admission to discharge (or most recently before in-hospital death) was also used. Correction of hyponatraemia was defined as a change in natraemia status from hyponatraemia on admission to no hyponatraemia (serum sodium concentration ≥135 mmol/L) at discharge.

To assess if admission hyponatraemia was a predictor of in-hospital endpoints (in-hospital death, New York Heart Association [NYHA] class III–IV at discharge, weight reduction >2 kg during hospitalization, length of intensive cardiac care unit [ICCU] stay >2 days), we performed multivariable logistic regressions with these outcomes as dependent variables, and with variables in *Tables 1* and *2* as independent variables. Hosmer–Lemeshow goodness of fit test was performed for the logistic regression models and was not statistically significant for all models except length of stay and ICCU stay.

Post-discharge, long-term outcomes analyses were performed excluding patients who died in hospital and those without any follow-up information. Mortality at 12 months (as percentage) was estimated using the Kaplan–Meier method. Cumulative incidence curves were plotted for the primary (all-cause death or first HF rehospitalization) and secondary endpoint (all-cause death) in the four natraemia groups, and multivariable Cox proportional hazards regressions were used to model the time to first event. Incidence (number of events per 100 patient-years) of the primary, secondary and tertiary endpoints was calculated for the four natraemia groups. Time was from date of discharge and censored at death not defined as an event or at end of follow-up. Adjustment was performed for variables in *Tables 1* and *2* together with cause of HF decompensation.

Missing data for the covariates included in the models were imputed with multiple imputation using Multivariate Imputation by Chained Equations (MICE)[18] with 10 datasets and 10 iterations. Variables included in the imputation model are indicated in *Tables 1* and *2*. The primary outcome, all-cause death or first rehospitalization for HF at follow-up, was included as the Nelson–Aalen estimator. Natraemia was not included in the model, nor was it imputed since patients with missing values were excluded from this analysis. For patients with missing information on the date of follow-up hospitalization, the time to hospitalization was imputed with half the time to last follow-up.

The level of significance was set to 0.05, two-sided, for all tests. All statistical analyses were conducted using R version 4.2.1 (2022-06-23)

Table 1 Baseline characteristics of acute heart failure patients with known admission and discharge sodium concentrations (*n* = 8298)

Variable	Hyponatraemia at admission/discharge				*p*-value
	Yes/Yes (*n* = 754, 9%)	Yes/No (*n* = 876, 11%)	No/Yes (*n* = 666, 8%)	No/No (*n* = 6002, 72%)	
Baseline clinical characteristics					
Age (years), median [IQR][a–c]	68 [59–78]	72 [62–80]	69 [59–78]	72 [62–79]	<0.001
Female sex (%)[a–c]	35	40	32	39	0.001
Body mass index (kg/m^2), median [IQR][a–c]	27 [25–30]	27 [25–31]	27 [25–31]	28 [25–31]	<0.001
Previous HF diagnosis (%)	80	68	72	68	<0.001
Previous HF hospitalization (%)	44	37	39	33	<0.001
Ischaemic HF aetiology (%)[a–c]	56	60	57	58	0.27
Hypertension (%)	54	67	62	70	<0.001
History of atrial fibrillation (%)	47	52	44	44	<0.001
Prior stroke or TIA (%)[a–c]	11	14	11	13	0.13
Peripheral vascular disease (%)[a–c]	13	18	17	15	0.02
Diabetes (%)[a–c]	42	43	36	38	0.007
Chronic kidney disease (%)	32	31	30	25	<0.001
Chronic obstructive pulmonary disease (%)[a–c]	19	23	20	20	0.14
Hepatic dysfunction (%)[a–c]	13	11	8.3	5.7	<0.001
History of thyroid dysfunction (%)[a–c]	12	12	12	9.8	0.058
Current malignant disease (%)[a–c]	4.2	7.1	5.3	5.2	0.06
Depression (%)[a–c]	9.2	11	9.0	7.5	0.003
Smoking (%)[a–c]	17	17	18	17	0.79
Previous pharmacotherapy (before hospital admission)					
Loop diuretic (%)	67	61	62	54	<0.001
Daily dose of loop diuretic >40 mg equivalent furosemide dose (%)[a,d]	32	29	26	18	<0.001
Thiazide diuretic (%)[a]	13	12	9.9	11	0.18
Mineralocorticoid receptor antagonist (%)[a]	49	35	41	29	<0.001
ACEi or ARB or ARNI (%)[a]	55	58	59	63	<0.001
Beta-blockers (%)[a]	56	56	59	57	0.67
Amiodarone (%)[a]	14	11	12	10	0.03
Other antiarrhythmic (%)[a]	3.9	3.4	3.6	3.6	0.98
Digoxin (%)[a]	28	20	19	15	<0.001
Calcium channel blockers (%)[a]	12	15	14	17	0.003
Antidepressants (%)[a]	6.8	9.6	6.3	7.0	0.03
Xanthine agents (%)[a]	1.9	1.0	0.3	1.5	0.03
NSAIDs (%)	5.7	3.9	3.6	4.6	0.20
Number of drugs with potential to cause hyponatraemia, median [IQR][e]	2 [1–3]	2 [1–3]	2 [1–3]	1 [0–2]	<0.001
Clinical presentation at admission					
Heart rate (bpm), median [IQR][a]	87 [72–105]	90 [75–110]	86 [73–100]	86 [72–104]	0.001
SBP (mmHg), median [IQR][a]	120 [100–140]	123 [110–140]	126 [110–142]	130 [117–150]	<0.001
Primary profile at presentation:[f]					<0.001
Cardiogenic shock (%)	3.1	3.5	2.7	2.0	
Pulmonary oedema (%)	12	15	15	13	
Decompensated HF (%)	69	62	63	62	
Right ventricular HF (%)	4.4	4.1	3.3	2.7	
NYHA class III/IV (%)[a]	87	82	84	79	<0.001
Pulmonary rales (%)	72	81	76	77	0.001
Peripheral oedema (%)	65	56	58	53	<0.001
Laboratory findings on admission					
Sodium (mmol/L), median [IQR][b]	131 [128–133]	133 [130–134]	137 [136–140]	140 [138–142]	<0.001
Potassium (mmol/L), median [IQR][a]	4.3 [3.8–4.8]	4.4 [3.9–4.8]	4.3 [3.9–4.7]	4.3 [3.9–4.7]	0.23
NT-proBNP (pg/ml), median [IQR][g]	6033 [2780–13 726]	5320 [1987–12 049]	4611 [1790–8480]	3797 [1730–8500]	<0.001
eGFR (ml/min/1.73 m^2), median [IQR][a,h]	57 [40–79]	52 [35–72]	59 [42–80]	62 [43–82]	<0.001
Urea (mg/dl), median [IQR][g]	40 [24–66]	39 [24–66]	37 [23–57]	31 [20–50]	<0.001
Bilirubin (mg/dl), median [IQR][g]	1.1 [0.8–1.8]	0.9 [0.6–1.5]	0.9 [0.6–1.4]	0.8 [0.6–1.2]	<0.001
Haemoglobin (g/dl), median [IQR][a]	12.0 [10.6–13.7]	12.3 [10.7–13.9]	12.7 [11.2–14.3]	12.9 [11.4–14.2]	<0.001
Electrocardiogram during hospitalization[h]					
Heart rhythm[a–c,f]					<0.001
Sinus rhythm (%)	53	53	59	59	
Atrial fibrillation/flutter (%)	35	36	32	33	
Other (%)	12	11	9.1	8.6	
Left bundle branch block (%)[i]	20	14	17	14	<0.001
Corrected QT interval (ms), median [IQR][i]	424 [365–463]	425 [379–462]	431 [392–466]	421 [372–456]	0.001

Table 1 (Continued)

Variable	Hyponatraemia at admission/discharge				*p*-value
	Yes/Yes ($n = 754$, 9%)	**Yes/No ($n = 876$, 11%)**	**No/Yes ($n = 666$, 8%)**	**No/No ($n = 6002$, 72%)**	
Echocardiogram during hospitalization[i]					
EF (%), median [IQR][a–c,g]	35 [25–45]	39 [28–51]	35 [25–47]	40 [30–52]	<0.001
EF category (%)[i]					<0.001
≤40%	68	57	66	54	
41–49%	11	12	9.6	14	
≥50	21	31	24	33	
LVEDD (mm), median [IQR][i]	60 [54–68]	59 [51–65]	60 [53–67]	58 [52–64]	<0.001
Restrictive/pseudonormal mitral inflow pattern (%)[i]	46	40	32	36	<0.001
Aortic stenosis moderate-severe (%)[a,c,i]	12	11	8.8	11	0.42
Mitral regurgitation moderate-severe (%)[a,c,i]	61	56	55	53	0.002
Tricuspid regurgitation moderate-severe (%)[a,c,i]	46	38	40	34	<0.001

The study population included all patients with serum sodium available at admission and at discharge. It included patients who died in hospital (3.3%), where the last available serum sodium value was used. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

[a]Variables included in multivariate logistic regression analyses of predictors of in-hospital outcomes and predictors of hyponatraemia on admission. Apart from those variables, cause of HF decompensation was also included.

[b]Variables included in multivariate logistic regression analysis of correction of hyponatraemia during hospitalization. Apart from those variables, cause of HF decompensation (acute coronary syndrome/myocardial ischaemia vs. arrhythmic vs. other), as well as % change in SBP and % change in eGFR during hospitalization were also included.

[c]Variables included in multivariate Cox proportional hazard analyses of predictors of long-term outcomes. Apart from those variables, cause of HF decompensation was also included.

[d]Furosemide 40 mg equivalent to torsemide 10 mg equivalent to bumetanide 1 mg.

[e]Loop and thiazide diuretics, mineralocorticoid receptor antagonists, antidepressants, amiodarone and other antiarrhythmic, xanthine agents.

[f]Mutually exclusive (only one option could be chosen for each patient).

[g]Data on NT-proBNP missing for 75% of patients, on urea for 21%, on bilirubin for 29%, on left bundle branch block for 5%, on corrected QT interval for 25%, on EF for 20%, on LVEDD for 25%, on mitral inflow pattern for 47%, on valvular heart disease for 19%.

[h]Based on the Chronic Kidney Disease Epidemiology Collaboration equation.

[i]Performed at any time point during hospitalization.

(R Core Team 2019). The R code used for the data handling and statistical analyses is found https://github.com/KIHeartFailure/eschyponatremia.

Results

Study population

A total of 25 621 patients were included in the ESC-HFA EORP HF Long-Term Registry from March 2011 to September 2018, including 10 879 patients hospitalized for AHF (online supplementary *Figure S1*). Of these, 9982 patients (92%) had available data on sodium concentration on hospital admission, and 8298 (76%) had available data both at admission and discharge (or before in-hospital death). Prevalences were: hyponatraemia Yes/Yes (754 patients, 9%), hyponatraemia Yes/No (876 patients, 11%), hyponatraemia No/Yes (666 patients, 8%), and hyponatraemia No/No (6002 patients, 72%) (*Graphical Abstract*).

Predictors of hyponatraemia at hospital admission

Of 8298 patients, 1630 (20%) had hyponatraemia at hospital admission, including mild (130–134 mmol/L) in 1205 (15%), moderate (125–129 mmol/L) in 285 (3.4%), and severe hyponatraemia (<125 mmol/L) in 140 (1.7%) patients.

As shown in online supplementary *Table S1*, admission hyponatraemia was independently associated with younger age, but otherwise markers associated with more advanced HF (lower body mass index, history of diabetes and hepatic disease, higher heart rate, and lower systolic blood pressure [SBP], eGFR and haemoglobin at hospital admission, as well as pharmacotherapy [at presentation] with thiazide diuretics, mineralocorticoid receptor antagonists [MRA], and digoxin, and doses of loop diuretics higher than equivalent to 40 mg of furosemide). Previous pharmacotherapy with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin receptor–neprilysin inhibitor (ARNI) and beta-blockers was associated with lower risk of admission hyponatraemia. Lower EF and higher New York Heart Association (NYHA) class at admission were not predictors of admission hyponatraemia (although there was a trend for EF).

Association of admission hyponatraemia with in-hospital outcomes

Of 8298 patients, 270 (3.3%) died during hospitalization (5.8% of patients with hyponatraemia on admission vs. 2.6% of patients with no hyponatraemia at admission). In multivariable logistic regression analysis, hyponatraemia at hospital admission was an independent predictor of in-hospital death (crude odds ratio [OR] 2.30, 95% confidence interval [CI] 1.78–2.97, $p < 0.001$, and adjusted OR 1.52, 95% CI 1.16–2.01, $p = 0.003$). Hyponatraemia on admission was also independently associated with NYHA class III–IV (vs. NYHA class I–II) at hospital discharge (adjusted OR 1.20, 95% CI 1.04–1.38, $p = 0.02$) and ICCU stay longer than 2 days (adjusted

Table 2 In-hospital treatment, clinical course of hospitalization and in-hospital outcomes of acute heart failure patients with known admission and discharge sodium concentrations ($n = 8298$)

Variable	Hyponatraemia at admission/discharge				p-value
	Yes/Yes ($n = 754$)	Yes/No ($n = 876$)	No/Yes ($n = 666$)	No/No ($n = 6002$)	
In-hospital management					
Inotropic support (%)[a,b]	22	18	18	9.0	<0.001
Nitrates i.v. (%)	21	20	22	19	0.32
Diuretics i.v. (%)	88	89	86	82	<0.001
Daily dose of loop diuretic >80 mg equivalent furosemide dose (%)[a,c,d]	41	35	32	26	<0.001
Thiazide diuretic (%)[a]	11	7.5	9.5	6.7	<0.001
Mineralocorticoid receptor antagonist (%)[a]	70	57	67	55	<0.001
ACEi or ARB or ARNI (%)[a]	68	71	75	79	<0.001
Beta-blockers (%)[a]	68	73	76	77	<0.001
Amiodarone (%)[a]	21	18	22	16	<0.001
Other antiarrhythmic (%)[a]	4.5	4.9	5.1	4.5	0.89
Digoxin (%)[a]	35	27	28	22	<0.001
PCI/CABG during hospitalization (%)[b]	7.2	12	12	12	0.002
In-hospital outcomes					
In-hospital death (%)	6.9	4.9	4.7	2.4	<0.001
Length of ICCU stay >2 days (%)	44	40	38	31	<0.001
Length of hospital stay >7 days (%)	50	55	61	48	<0.001
Improvement in NYHA class during hospitalization (%)[a]	74	79	79	76	0.07
Reduction in weight in % during hospitalization, median [IQR][a]	2.4 [4.9–0.0]	2.5 [4.6–0.0]	2.7 [5.3–0.0]	2.0 [4.0–0.0]	<0.001
Reduction in weight >2 kg during hospitalization (%)	39	40	43	32	<0.001
Clinical findings at discharge or prior to in-hospital death					
NYHA class III–IV at discharge (%)[a,b]	34	26	27	22	<0.001
Residual congestion (%)[a,b] defined as at least one of the following	46	38	30	32	<0.001
Pulmonary rales (%)	18	18	14	14	0.004
Increased jugular venous pressure (%)	13	9.7	6.1	6.4	<0.001
Pleural effusion (%)	12	10	5.8	7.8	<0.001
Hepatomegaly (%)	20	14	12	11	<0.001
Peripheral oedema (%)	19	17	13	11	<0.001
Heart rate (bpm), median [IQR][b]	73 [66–82]	72 [66–80]	70 [65–80]	70 [65–80]	0.001
SBP (mmHg), median [IQR][b]	110 [100–120]	117 [106–130]	114 [103–125]	120 [110–130]	<0.001
Laboratory findings at discharge or prior to in-hospital death					
Sodium (mmol/L), median [IQR]	132 [129–133]	138 [136–140]	133 [131–134]	140 [138–142]	<0.001
Potassium (mmol/L), median [IQR][b]	4.3 [3.9–4.7]	4.2 [3.9–4.6]	4.3 [4.0–4.7]	4.3 [4.0–4.6]	0.01
NT-proBNP (pg/ml), median [IQR][d]	4370 [1942–8757]	2367 [1036–8373]	2486 [837–5878]	1987 [920–4863]	<0.001
Absolute change in NT-proBNP during hospitalization (pg/ml), median [IQR][d,e]	−540 [−3146 to 0]	−930 [−4593 to 0]	−943 [−3653 to −49]	−970 [−3662 to 0]	0.62
eGFR (ml/min/1.73 m^2), median [IQR][b,f]	59 [41–80]	57 [41–76]	56 [38–76]	61 [43–80]	<0.001
Absolute change in eGFR during hospitalization (ml/min/1.73 m^2), median [IQR]	0.0 [−5.0 to 7.4]	2.2 [−3.9 to 12.1]	−1.0 [−10.8 to 6.0]	0.0 [−6.1 to 5.3]	<0.001
Haemoglobin (g/dl), median [IQR][b,d]	12.0 [10.7–13.5]	12.1 [10.8–13.5]	12.4 [11.0–14.0]	12.7 [11.2–14.0]	<0.001
Pharmacotherapy at discharge					
Loop diuretic (%)	86	84	86	82	<0.001
Daily dose of loop diuretic >40 mg equivalent furosemide dose (%)[b,c]	63	57	55	45	<0.001
Thiazide diuretic (%)	9.6	7.3	8.3	8.1	0.42
Mineralocorticoid receptor antagonist (%)[b]	67	57	64	54	<0.001
ACEi or ARB or ARNI (%)[b]	67	70	73	79	<0.001
Beta-blockers (%)[b]	68	74	76	78	<0.001
Amiodarone (%)[b]	18	16	19	14	0.004
Other antiarrhythmic (%)	4.2	3.8	4.5	3.8	0.76
Digoxin (%)	32	25	25	20	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; ICCU, intensive cardiac care unit; IQR, interquartile range; i.v., intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

[a]Variables included in multivariate logistic regression analysis of correction of hyponatraemia during hospitalization. Apart from those variables, cause of HF decompensation (acute coronary syndrome/myocardial ischaemia vs. arrhythmic vs. other), as well as % change in SBP and % change in eGFR during hospitalization were also included.

[b]Variables included in multivariate Cox proportional hazard analyses of predictors of long-term outcomes. Apart from those variables, cause of HF decompensation was also included.

[c]Furosemide 40 mg equivalent to torsemide 10 mg equivalent to bumetanide 1 mg.

[d]Data on loop diuretic dose during hospitalization missing for 20% of patients, on NT-proBNP for 89%, on NT-proBNP change for 91%, on haemoglobin for 10%, on loop diuretic dose at discharge for 18%.

[e]A negative value reflects a reduction.

[f]Based on the Chronic Kidney Disease Epidemiology Collaboration equation.

OR 1.50, 95% CI 1.32–1.71, $p < 0.001$), but importantly, also with weight reduction of more than 2 kg during hospitalization (adjusted OR 1.24, 95% CI 1.09–1.40, $p = 0.001$).

Predictors of correction of hyponatraemia during hospitalization

Of 1630 patients with hyponatraemia at hospital admission, 876 (54%) corrected hyponatraemia during hospitalization (hyponatraemia Yes/No). Median change in sodium concentration in the persisting hyponatraemia (Yes/Yes) group was 0.0 (IQR −1.0–2.9) mmol/L and in the corrected hyponatraemia (Yes/No) group it was 6.0 (IQR 4.0–9.0) mmol/L ($p < 0.001$). Independent predictors of correction of hyponatraemia during hospitalization are shown in online supplementary *Table S2* and included higher admission serum sodium level (i.e. closer to the threshold for normalization), greater improvement in NYHA class and eGFR during hospitalization, and in-hospital beta-blocker therapy. Residual congestion at discharge and treatment with MRA during hospitalization were independent predictors of persisting hyponatraemia. Neither lower EF, SBP change during hospitalization, nor in-hospital treatment with high doses of loop diuretics (i.e. above 80 mg equivalent furosemide dose) were associated with persisting hyponatraemia.

Comparison of the four natraemia groups

Baseline characteristics

Table 1 and *Figure 1* present comparison of the four natraemia groups with respect to baseline characteristics. Compared to the reference group (hyponatraemia No/No), patients who were hyponatraemic on admission or who progressed to hyponatraemia during hospitalization were younger, more often male, had lower body mass index, less often had hypertension, and more often diabetes, chronic kidney disease, hepatic and thyroid dysfunction, had more advanced HF (with lower EF, larger left ventricle, higher NYHA class, more mitral and tricuspid regurgitation), were more often treated with loop diuretics, MRA and digoxin, and less often with ACEi/ARB/ARNI before hospitalization, and had higher N-terminal pro-B-type natriuretic peptide (NT-proBNP), more peripheral oedema, lower SBP, lower haemoglobin, and worse kidney and hepatic function on admission. Patients with hyponatraemia on admission (hyponatraemia Yes/Yes and hyponatraemia Yes/No) more often presented with cardiogenic shock and right ventricular HF, and with infection as a precipitating factor. Patients with persisting hyponatraemia (hyponatraemia Yes/Yes) less often presented with acute coronary syndrome/myocardial ischaemia as a cause of HF decompensation, while those with corrected hyponatraemia (hyponatraemia Yes/No) more often had an arrhythmic cause of HF exacerbation.

Clinical course of hospitalization

Table 2 and *Figure 1* show comparison of the four natraemia groups with respect to clinical course of hospitalization and in-hospital outcomes. Patients with hyponatraemia Yes/Yes had the highest in-hospital mortality: 6.9% versus 4.9% in Yes/No, 4.7% in No/Yes, and 2.4% in No/No, $p < 0.001$ (OR and 95% CI vs. No/No [reference] group: Yes/Yes OR 3.01, 95% CI 2.17–4.18, $p < 0.001$; Yes/No OR 2.10, 95% CI 1.48–2.97, $p < 0.001$, and No/Yes OR 1.99, 95% CI 1.34–2.96, $p = 0.001$). Patients with hyponatraemia Yes/Yes also had the longest ICCU stay, the worse clinical status at hospital discharge, and the smallest reduction in NT-proBNP, while the reference group (hyponatraemia No/No) had the lowest in-hospital mortality, the shortest ICCU stay, the best clinical status at discharge, and the largest reduction in NT-proBNP. Patients with hyponatraemia Yes/No had the greatest improvement in eGFR. Hyponatraemia No/Yes had the largest reduction in weight during hospitalization. Hyponatraemia Yes/Yes and No/Yes more often received MRA and thiazide diuretics, and received higher doses of loop diuretics.

Post-discharge, long-term outcomes in relation to the natraemia group

Of 8298 AHF patients, 270 (3.3%) died during hospitalization and 2283 (28%) were lost to follow-up, leaving 5745 patients (69%) for the analysis of post-discharge, long-term outcomes. Median follow-up was 12.1 months (IQR 10.9–13.8 months) with a total of 6016 patient-years of follow-up. Mortality at 12 months was 19% (95% CI 18–20%). The incidence of the primary endpoint (all-cause death or first HF hospitalization) per 100 patient-years (95% CI) was 73 (64–82) in the hyponatraemia Yes/Yes, 54 (48–61) in the hyponatraemia Yes/No, 47 (41–55) in the hyponatraemia No/Yes, and 38 (36–40) in the hyponatraemia No/No group. The incidence of the secondary endpoint (all-cause death) per 100 patient-years (95% CI) was 40 (34–46) in the hyponatraemia Yes/Yes, 31 (26–35) in the hyponatraemia Yes/No, 24 (19–28) in the hyponatraemia No/Yes, and 19 (17–20) in the hyponatraemia No/No group.

Figure 2 shows cumulative incidence curves and adjusted hazard ratios (HR, 95% CI) for the primary and secondary endpoint in relation to the natraemia group. Patients with hyponatraemia persisting during hospitalization (hyponatraemia Yes/Yes) had a 38% higher risk of the primary endpoint (all-cause death or first HF hospitalization) and a 60% higher risk of the secondary endpoint (all-cause death) compared to the reference group (hyponatraemia No/No). Patients who corrected admission hyponatraemia during hospitalization (hyponatraemia Yes/No) had a 17% higher risk of the primary endpoint, and a 35% higher risk of the secondary endpoint compared to the reference group. Interestingly, patients who developed hyponatraemia during hospitalization (hyponatraemia No/Yes) did not have greater risk of the primary or secondary endpoints than the reference group.

Figure 3 shows adjusted HR (95% CI) for the tertiary endpoints in respective natraemia groups. Hyponatraemia both at admission and at discharge was associated with cardiovascular and HF death but, interestingly, not with all-cause hospitalization, first cardiovascular hospitalization or first HF hospitalization.

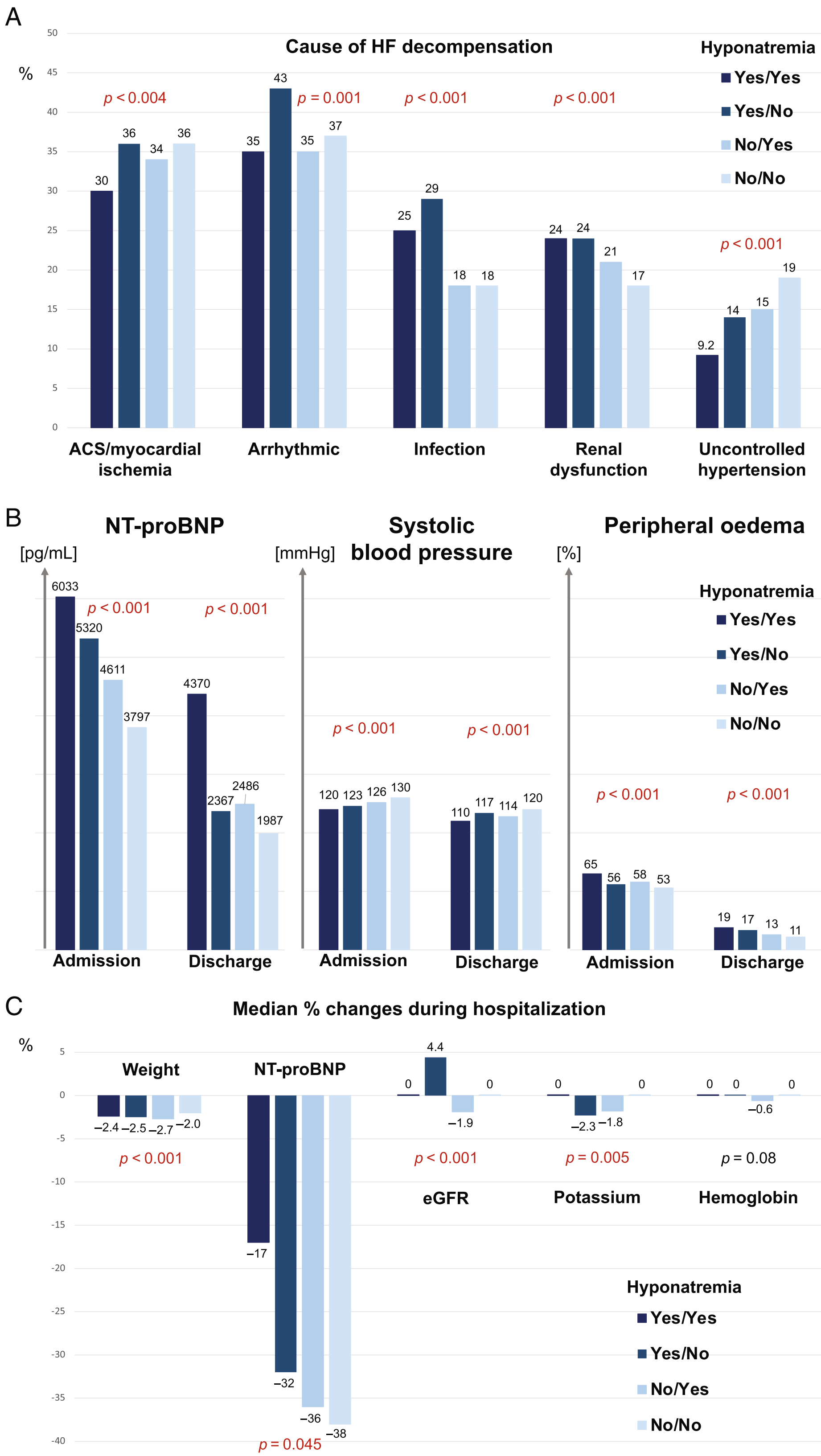


Figure 1 Continued

Discussion

In this large contemporary AHF study, the main findings were: (i) hyponatraemia at admission was present in 20%, was associated with more advanced HF, and resolved in half; (ii) admission hyponatraemia and especially persistent hyponatraemia were strongly associated with in-hospital and post-discharge death; (iii) 8% developed hyponatraemia during hospitalization, possibly as a result of an intensive diuretic treatment (higher doses of loop diuretics, combination with other diuretics) leading to natri-/diuresis, decongestion and depletional hyponatraemia; (iv) hyponatraemia developing *de novo* during hospitalization was not associated with significantly increased risk of post-discharge death. One novel aspect of our work was showing that *de novo* hyponatraemia during intensive in-hospital diuretic therapy leading to decongestion might not negatively affect long-term prognosis, analogously to previous data suggesting that worsening eGFR during AHF is not associated with adverse outcomes if accompanied by decongestion.[19,20]

Associations with hyponatraemia at admission and sodium changes during hospitalization

The 20% prevalence of hyponatraemia at hospital admission is consistent with previous studies.[1–10] Hyponatraemia in HF is generally dilutional and increases with the severity of HF.[5,6,21] In our analysis of a large number of potential risk markers, we confirm the association with more advanced HF but offer some granular observations. In general, factors associated with admission and persistent hyponatraemia were markers associated with more advanced HF such as haemodilution, lower SBP, EF and eGFR, higher NYHA class and NT-proBNP, larger left ventricular diameter, more mitral and tricuspid regurgitation and more restrictive/pseudonormal mitral inflow pattern. There were strong association with right-sided HF (oedema, pleural effusion, increased jugular venous pressure, hepatomegaly, hepatic dysfunction, higher bilirubin concentration) and less with left-sided HF (pulmonary rales, pulmonary oedema at presentation). Thus, hyponatraemia seems to be associated with HF due to fluid overload (right-sided HF) rather than with HF due to fluid redistribution (left-sided HF). This highlights the growing understanding of right-sided HF, especially when reaching the stage of hepatic dysfunction, as a critical prognostic factor in HF.[22,23] Importantly, all congestion markers were individually associated with hyponatraemia, suggesting that they are additive. In contrast, EF and NYHA class were not independent risk markers of admission hyponatraemia, suggesting that hyponatraemia is mediated not by EF or HF severity itself, but rather by right-sided HF, fluid overload and congestion, as well as kidney and liver dysfunction.[22–24]

Association between hyponatraemia and in-hospital and post-discharge outcomes

Patients with persisting hyponatraemia had the highest in-hospital mortality and if they survived to hospital discharge, also the worst post-discharge outcomes, with all-cause mortality 60% higher than the reference group. In-hospital and post-discharge mortality with corrected hyponatraemia (Yes/No) was in-between persisting (Yes/Yes) and patients with no hyponatraemia throughout hospitalization (No/No), suggesting, not surprisingly, that hyponatraemia resolving in response to therapy is a favourable prognostic sign.

Patients who developed *de novo* hyponatraemia during hospitalization received intensive diuretic therapy and had the greatest reduction in weight and the lowest frequency of residual congestion, but at the cost of a decline in eGFR. Hence, the main cause of *de novo* hyponatraemia in this group appeared to be depletional rather than worsening congestion. In-hospital mortality was intermediate but interestingly, post-discharge all-cause death and all-cause death or HF hospitalization, as well as hospitalization for cardiovascular, HF, or any reason, was no worse than the reference group, while cardiovascular mortality and HF mortality was still worse than in the reference group. These findings are inconsistent and difficult to interpret but suggest that depletional hyponatraemia during HF hospitalization may not necessarily be as harmful as anticipated.

The association between reversal of hyponatraemia and improved survival has been reported previously.[3,10,25] In a recent study of 3628 AHF patients, with serum sodium concentrations measured every 6 h since admission, rapid changes in serum sodium (both rapid decline from hypernatraemia, and in contrast

Figure 1 (*A*) Cause of heart failure (HF) decompensation in relation to the natraemia group. Several causes may have contributed to decompensation and those listed here are not mutually exclusive. Arrhythmic cause included both atrial fibrillation and ventricular arrhythmia. More than one cause of HF decompensation could be chosen for each patient. (*B*) Selected clinical and laboratory parameters on admission and at discharge (or before in-hospital death) in acute HF in relation to the natraemia group. For N-terminal pro-B-type natriuretic peptide (NT-proBNP) and systolic blood pressure results are shown as median, for peripheral oedema as %. Data on NT-proBNP on admission are missing for 75% of patients, and at discharge for 89%. (*C*) Median percent changes in weight and laboratory parameters during hospitalization for acute HF in relation to the natraemia group. A negative value reflects a reduction, and a positive value reflects an increase during hospitalization. For NT-proBNP data are missing for 91% of patients; for haemoglobin for 11%. *P*-value for difference between natraemia groups. Analysis included all patients hospitalized for acute HF with known admission and discharge sodium concentrations ($n = 8298$). ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate (based on the Chronic Kidney Disease Epidemiology Collaboration equation); hyponatraemia Yes/Yes, hyponatraemia at hospital admission and at discharge; hyponatraemia Yes/No, hyponatraemia at hospital admission, no hyponatraemia at discharge; hyponatraemia No/Yes, no hyponatraemia at hospital admission, hyponatraemia at discharge; hyponatraemia No/No, hyponatraemia neither at hospital admission nor at discharge.

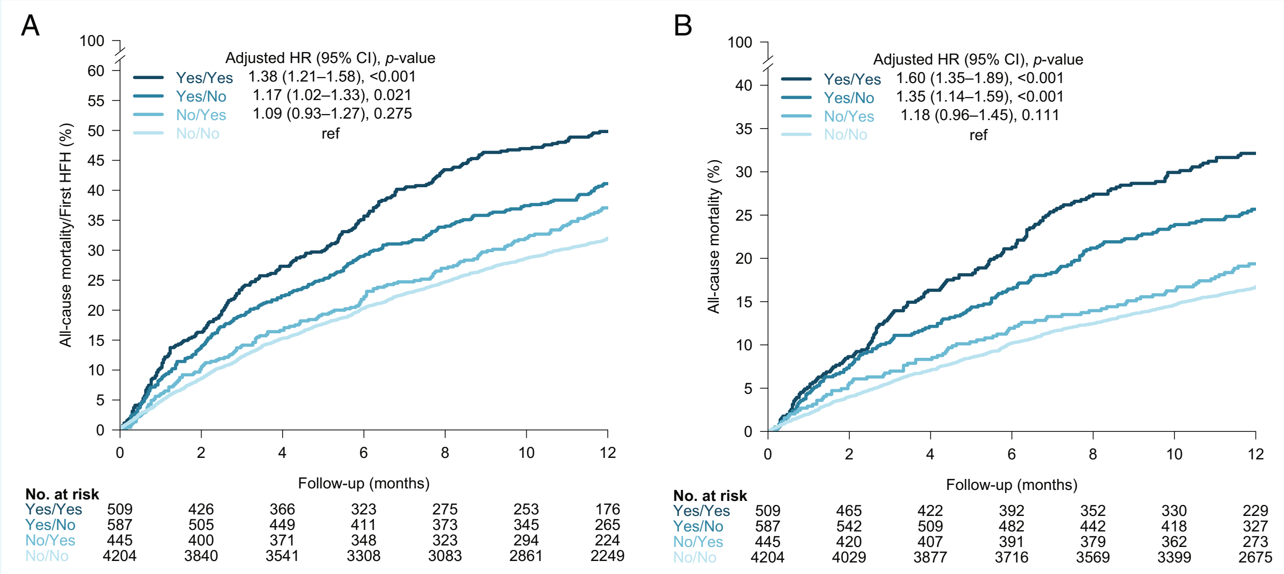


Figure 2 Cumulative incidence curves and adjusted hazard ratios (HRs) for the primary (*A*) and the secondary endpoint (*B*) in acute heart failure in relation to the natraemia group. (*A*) All-cause death or first heart failure hospitalization (HFH). (*B*) All-cause death. CI, confidence interval; HFH, heart failure hospitalization; HR, hazard ratio; Yes/Yes, hyponatraemia at hospital admission and at discharge; Yes/No, hyponatraemia at hospital admission, no hyponatraemia at discharge; No/Yes, no hyponatraemia at hospital admission, hyponatraemia at discharge; No/No, hyponatraemia neither at hospital admission nor at discharge.

Outcome	Hyponatremia	Adjusted HR (95% CI), *p*-value
CV mortality	Yes/Yes	1.58 (1.24–2.00), <0.001
	Yes/No	1.43 (1.14–1.79), 0.002
	No/Yes	1.49 (1.15–1.93), 0.003
	No/No	ref
HF mortality	Yes/Yes	1.44 (1.07–1.93), 0.016
	Yes/No	1.38 (1.05–1.81), 0.020
	No/Yes	1.38 (1.00–1.90), 0.051
	No/No	ref
First hospitalisation	Yes/Yes	1.11 (0.96–1.28), 0.159
	Yes/No	1.07 (0.94–1.22), 0.327
	No/Yes	0.98 (0.84–1.15), 0.820
	No/No	ref
First CV hospitalisation	Yes/Yes	1.08 (0.92–1.27), 0.343
	Yes/No	0.97 (0.84–1.13), 0.729
	No/Yes	0.98 (0.83–1.16), 0.831
	No/No	ref
First HF hospitalisation	Yes/Yes	1.13 (0.94–1.35), 0.185
	Yes/No	1.04 (0.87–1.23), 0.685
	No/Yes	1.08 (0.89–1.30), 0.452
	No/No	ref

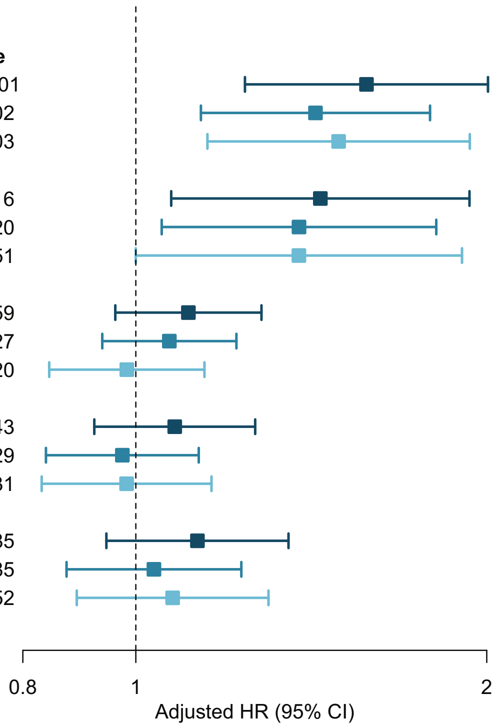


Figure 3 Association of the natraemia group with the tertiary endpoints after discharge from an acute heart failure (HF) hospitalization. CI, confidence interval. CV, cardiovascular; HR, hazard ratio; Yes/Yes, hyponatraemia at hospital admission and at discharge; Yes/No, hyponatraemia at hospital admission, no hyponatraemia at discharge; No/Yes, no hyponatraemia at hospital admission, hyponatraemia at discharge; No/No, hyponatraemia neither at hospital admission nor at discharge.

to in our study, rapid increase from hyponatraemia) were related to increased 1-year mortality but in this case conceivably, the rapidity of change may have been a marker of underlying severity of sodium derangements.[26]

Notably, in our study, the association of hyponatraemia with long-term outcomes was observed only for mortality (all-cause, cardiovascular and HF), but not for first hospitalizations (all-cause, cardiovascular or HF). Lack of association between hyponatraemia and subsequent HF hospitalizations could be partially explained by more intensive diuretic treatment of hyponatraemic patients at hospital discharge compared to the reference group. Still, this observation requires further investigation.

Diuretic treatment, especially with agents that block sodium resorption in the distal parts of the nephron (such as MRAs and thiazide diuretics), is known to be associated with depletional hyponatraemia which has been assumed to be harmful.[5,13,27] In our study, more intensive diuretic treatment was indeed associated with the development of in-hospital, *de novo* hyponatraemia, but this was not associated with significantly increased post-discharge all-cause mortality. Aggressive diuresis during hospitalization may be a risk marker for greater severity of HF (greater perceived need of diuretics) but a protective factor, that is, causative in achieving decongestion and reducing post-discharge risk. Indeed, in the DOSE trial, there was no difference between loop diuretic bolus or infusion, but there was a tendency toward greater benefits with higher versus lower doses.[28] Aggressive diuresis may cause worsening eGFR, as it did in our study, but this is often transient and lowering eGFR may be associated with benefit if it occurs in conjunction with effective decongestion.[19,20] ACEi/ARB/ARNI and beta-blocker use was associated with lower risk of admission hyponatraemia, and in-hospital treatment with beta-blockers was associated with correction of admission hyponatraemia. ACEi, ARB and ARNI have a known protective effect against dilutional hyponatraemia by antagonizing angiotensin II constrictor effect on glomerular arteriole and vasopressin effects through reducing aquaporin-2 expression in the collecting ducts. ARNI additionally exert their favourable effects via natriuretic peptides, which, in contrast to ACEi and ARB, dilate predominantly the afferent glomerular arteriole.[5,29] Our registry was conducted in years 2011–2018, before the introduction of sodium–glucose contrasporter 2 inhibitors (SGLT2i) to the standards of treatment for HF with reduced EF. In HF, SGLT2i have favourable effects on cardiac remodelling and stroke volume, which on its own prevents dilutional hyponatraemia. Given that SGLT2i block sodium reabsorption in the proximal nephron and induce osmotic diuresis, they may exert additional protective effects against hyponatraemia.[5] A wider use of another proximally-acting diuretic, acetazolamide (e.g. instead of distally-acting thiazides) in the decongestive treatment of AHF, might also decrease the risk of hyponatraemia and hypochloraemia – another important, though so far neglected prognostic factor in AHF.[5,30]

Limitations

In this observational survey, data on serum sodium concentration on admission were missing for 8% and for admission or discharge for 24%. These patients were excluded which may be associated with selection bias. There were also some other data missing. To reduce bias due to data missing not being random, and thus to increase generalizability, we used multiple imputation. Serum sodium is a continuous variable. The cut-off used is universally accepted but may limit the numerical resolution in our results. The exact timing of discharge serum sodium measurement was not specified in the registry. In the registry, there was no information on the use of tolvaptan, hypertonic saline solution or any other measures taken specifically to treat hyponatraemia in HF. No data were collected on serum chloride concentration. As mentioned above, the survey was conducted in years 2011–2018, before the introduction of SGLT2i to HF therapy. All results are associations, and in particular for changes during hospitalization, such as changes in sodium, eGFR, and weight, it is not possible to establish causality.

Conclusions

In AHF, 20% of patients had hyponatraemia at hospital admission, and in half of them hyponatraemia resolved during hospitalization. Admission hyponatraemia (possibly mainly dilutional) was associated with more advanced HF, and, especially if it persisted during hospitalization, was associated with worse in-hospital and post-discharge outcomes. Hyponatraemia developing during hospitalization (possibly depletional as a result of intensive diuretic treatment and appropriate decongestion) was associated with lower risk.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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