ORIGINAL ARTICLE

Clinical characteristics and 1-year outcome of hyponatremic patients hospitalized for heart failure

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KEY WORDS

heart failure, hospitalization, hyponatremia, prognosis, sodium

ABSTRACT

INTRODUCTION Previous studies have shown that hyponatremia is associated with unfavorable prognosis in patients with heart failure (HF). However, only few studies aimed at the evaluation of long-term outcome in hyponatremic patients hospitalized for HF.

OBJECTIVES The aim of this study was to assess clinical characteristics and 1-year outcome of patients hospitalized for HF with hyponatremia at hospital admission.

PATIENTS AND METHODS The study included 641 Polish participants of the HF Pilot Survey of the European Society of Cardiology. The primary endpoint was all-cause death at 1 year since index hospitalization. The secondary endpoint was all-cause death or rehospitalization for decompensated HF during a 1-year follow-up.

RESULTS Hyponatremia occurred in 15.8% of 641 patients. On admission, hyponatremic patients were characterized by a higher New York Heart Association class, lower blood pressure, lower body mass index, and higher creatinine and lower hemoglobin concentrations on admission. Compared with normonatremic individuals, hyponatremic patients were at a higher risk of in-hospital death (1.9% vs 9.9%, $P < 0.0001$), death at 1 year (10.4% vs 31.7%; $P < 0.0001$), and death or rehospitalization at 1 year (35.9% vs 56.5%; $P < 0.0001$). In multivariate analyses, hyponatremia was predictive of both the primary (hazard ratio [HR], 3.07; 95% confidence interval [CI], 1.94–4.87; $P < 0.0001$) and secondary endpoints (HR, 1.71; 95% CI, 1.16–2.52; $P = 0.007$). Hyponatremia was an independent predictor of the primary endpoint also in a subgroup of 621 patients who survived to hospital discharge (HR, 2.11; 95% CI, 1.15–3.86; $P = 0.02$).

CONCLUSIONS Hyponatremia is a common finding in patients hospitalized for HF. Even in patients who survive to hospital discharge, hyponatremia on admission remains an independent predictor of death in long-term follow-up.

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INTRODUCTION Hyponatremia frequently coexists with advanced heart failure (HF).[1] Data from registries and clinical trials have demonstrated the association of hyponatremia with increased mortality and morbidity in patients hospitalized for HF.[2-14] However, only a few of those studies were designed to evaluate the effect of hyponatremia at hospital admission on long-term survival in patients successfully discharged after hospitalization for HF.[2,6,9] Furthermore, data on the prevalence of hyponatremia in Polish patients with HF are scarce, and there have been no studies assessing clinical characteristics and long-term prognosis of these patients.[15]

The Heart Failure Pilot Survey of the European Society of Cardiology (ESC-HF Pilot) was a prospective, multicenter registry of HF patients across Europe.[16,17] In our previous analysis of the Polish cohort of the ESC-HF Pilot, we discovered that a lower sodium concentration at

hospital admission was an independent predictor of in-hospital mortality.[18] The aim of this study was to evaluate the incidence of hyponatremia in Polish ESC-HF Pilot patients hospitalized for HF, to assess the clinical characteristics of those patients, and to investigate the effect of hyponatremia on 1-year outcome. Additionally, we sought to specifically investigate whether hyponatremia on admission was predictive of 1-year outcome in patients who survived to hospital discharge.

PATIENTS AND METHODS

Study population

The ESC-HF Pilot was a prospective, multicenter, observational survey of HF patients conducted from October 2009 to May 2010 in 136 European cardiology centers, including 29 centers in Poland.[16,17] The survey included patients admitted to the hospital for new-onset or worsening HF, as well as outpatients with HF seen in ambulatory care. Eligible patients were enrolled if they were at least 18 years of age and met diagnostic criteria for HF. There were no specific exclusion criteria.

Data regarding demographic characteristics, medical history, clinical presentation, diagnostic test results, previous and current treatment, clinical course of index hospitalization (in case of inpatients), as well as 1-year follow-up were collected.

The survey was approved by the local ethical review board. All patients were provided with detailed information on the aim, scope, and methodology of the study, and all signed written informed consent.

The current analysis included Polish participants of the ESC-HF Pilot who were hospitalized for HF (outpatients seen in ambulatory care were excluded from the study). All patients with available data on serum sodium concentrations on admission were included in the analysis.

Comparative analysis of normo- and hyponatremic patients

Hyponatremia was defined as a serum sodium concentration of less than 135 mmol/l, and severe hyponatremia, as a serum sodium level of less than 130 mmol/l. Hypo- and normonatremic patients were compared with regard to baseline characteristics (demographic data, medical history, and previous pharmacotherapy), the course of index hospitalization (clinical status and laboratory findings at hospital admission and discharge, implementation of major therapeutic procedures during index hospitalization and the choice of discharge medication), in-hospital outcome (death during index hospitalization and length of hospital stay), and 1-year outcome (all-cause death and death or rehospitalization for decompensated HF).

Clinical endpoints at 1-year follow-up

The primary endpoint was all-cause death at 1 year. The secondary endpoint was a composite of all-cause death and hospital readmission for decompensated HF at 1 year.

To establish whether hyponatremia was an independent predictive factor of the primary and secondary endpoints, a number of explanatory variables were included in the univariate Cox proportional hazards regression analysis, including variables that were found to be prognostic for long-term outcome in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry (provided that they were available in the ESC-HF Pilot database).[19] Variables with data missing for 15% of the patients or more were excluded from the analysis.

The main goal of the study was to assess the relationship between hyponatremia and clinical endpoints at 1 year in the whole study group of hospitalized HF patients. In addition, we analyzed the predictors of the primary and secondary endpoints in a subgroup of patients successfully discharged after index hospitalization for HF (ie, patients who survived to hospital discharge), which allowed to include additional variables (other than baseline variables) in the Cox proportional hazards regression model. Those additional variables (proven to be important prognostic factors in the analysis of the OPTIMIZE-HF registry) were systolic blood pressure (SBP) at discharge and medications prescribed at discharge (including treatment with diuretics, aldosterone antagonists, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers, β-blockers, antiarrhythmic drugs, and statins).

All variables found to be statistically significant predictors in univariate analyses were then included in the multivariate models.

Statistical analysis

Categorical data were presented as a number of patients and percentages. For normally distributed continuous variables, mean value and standard deviation were used. Ordinal variables and nonnormally distributed continuous variables were presented as a median value and interquartile range (IQR). Comparisons between the groups were made using the Fisher exact test for categorical variables and the Mann–Whitney test for continuous and ordinal variables. Kaplan–Meier curves were plotted for the primary and secondary endpoints in both groups. To determine the predictors of the primary and secondary endpoints, the Cox proportional hazards regression model was used. Multivariate analyses included variables that were found to be statistically significant predictors in univariate analyses. Statistical significance was considered for a P value of less than 0.05 for all tests. Statistical analyses were performed using the SAS software, version 9.2 (SAS Institute, United States).

RESULTS

Study group selection

A total of 5118 patients were enrolled in the ESC-HF Pilot across Europe. The Polish cohort of the registry comprised 893 patients, including 650 inpatients. Nine patients with no data on serum sodium concentrations at hospital admission were excluded from the study, leaving 641 patients for the final analysis. Data on 1-year survival were available

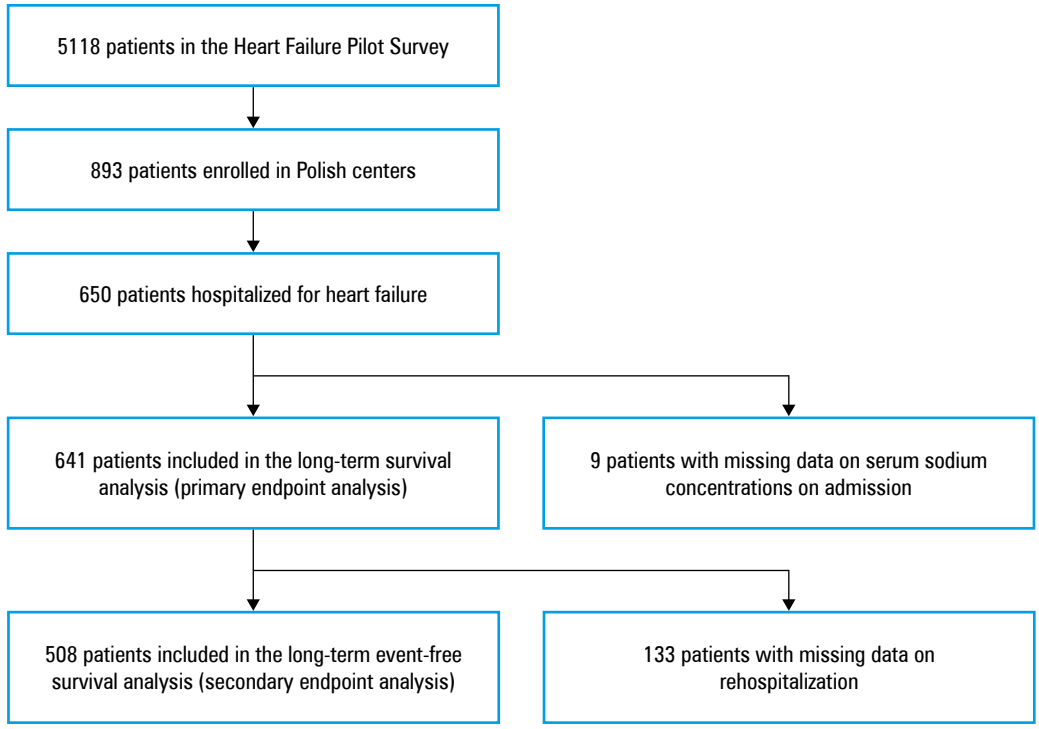


FIGURE 1 Flow chart of patient enrollment to the study

for all 641 patients. Data on rehospitalizations for decompensated HF were missing for 133 patients, leaving 508 patients (79.3% of 641 patients) for the secondary endpoint analysis. FIGURE 1 shows the flow chart of patient enrollment in the study.

Study group characteristics The median age in the whole study group (n = 641) was 69 years (IQR, 58–78 years), and 64.0% of the patients were male. Median left ventricular ejection fraction (LVEF) was 37% (IQR, 26.0%–49.5%), and HF with preserved LVEF was present in 25.0% of the patients. The etiology of HF encompassed ischemic HF in 61.2% of the patients, valvular heart disease in 11.4%, hypertensive HF in 10.8%, dilated cardiomyopathy in 9.4%, and tachycardia-induced cardiomyopathy in 1.9%. In the remaining 5.3% of the patients, the etiology of HF was not defined by the investigators. The causes of HF decompensation leading to index hospitalization included acute coronary syndrome in 30.1% of the patients, atrial fibrillation in 17.2%, uncontrolled hypertension in 14.4%, noncompliance to HF treatment in 14.1%, infection in 8.5%, renal dysfunction in 7.4%, anemia in 4.9%, ventricular arrhythmia in 4.7%, bradyarrhythmia in 3.3%, iatrogenic causes in 1.7%, and other causes in 39.3% (with a possibility to name more than 1 triggering factor of worsening HF for each patient).

Comparative analysis of normo- and hyponatremic patients The median serum sodium concentration on admission in the study group was 138.4 mmol/l (IQR, 136.0–141.0 mmol/l). Hyponatremia on admission was present in 101 of 641 patients (15.8%), including 14 patients (2.2% of the whole study group) with severe hyponatremia. Comparative characteristics of hypo- and normonatremic patients are presented in TABLE 1. Patients with hyponatremia on admission had a lower body mass index (BMI), were more often treated with aldosterone antagonists, and received higher doses of loop diuretics. On admission, hyponatremic patients were characterized by a worse clinical status (higher New York Heart Association [NYHA] class), lower systolic and diastolic blood pressure, and higher serum creatinine and lower hemoglobin concentrations. Hyponatremic patients were hospitalized longer, had lower SBP at discharge, and were at a higher risk of in-hospital death, as well as the occurrence of the primary and secondary endpoints at 1 year.

Primary endpoint Data on 1-year survival were available for all 641 patients. The primary endpoint occurred in 88 patients (13.7%), including 32 of 101 hyponatremic patients (31.7%) and 56 of 540 normonatremic patients (10.4%; $P < 0.0001$), as shown in TABLE 1. One-year survival probability in both groups is demonstrated by the Kaplan–Meier curves in FIGURE 2. The predictors of primary and secondary endpoints as shown by the univariate analysis are presented in TABLE 2. Hyponatremia was found to be predictive of the primary endpoint and remained an independent risk factor for death at 1 year in the multivariate Cox proportional hazards regression model (TABLE 3). Owing to the lack of complete data for some of the patients in the registry, the multivariate analysis included only those patients for whom all the required parameters were available (622 of 641 [97.0%]).

Secondary endpoint Data on hospital readmissions for decompensated HF were missing for 133 patients, leaving a total of 508 patients for the

TABLE 1 Baseline characteristics, clinical course of index hospitalization, and in-hospital and long-term outcomes of patients with and without hyponatremia at hospital admission

Characteristics	Serum sodium level on admission (n = 641)		*P* value
	normonatremia (n = 540)	hyponatremia (n = 101)	
demographic data			
age, y	70 (58–77); n = 540	69 (58–80); n = 101	0.67
male sex	64.3; 347/540	65.4; 66/101	0.91
BMI, kg/m^2	27.8 (24.8–31.6); n = 479	26.6 (23.3–29.6); n = 88	0.02
heart failure			
LVEF, %	37.0 (27.0–49.5); n = 472	35.0 (25.0–49.0); n = 88	0.39
HFPEF	25.0; 118/472	25.0; 22/88	1.00
previous HF hospitalization	57.2; 309/540	59.4; 60/101	0.74
medical history			
hypertension	66.9; 361/540	63.4; 64/101	0.49
coronary artery disease	59.6; 321/539	59.4; 60/101	1.00
prior PCI or CABG	33.2; 179/539	31.7; 32/101	0.82
history of atrial fibrillation	39.4; 212/538	36.6; 37/101	0.66
peripheral artery disease	9.1; 49/540	8.9; 9/101	1.00
diabetes	34.3; 185/540	42.6; 43/101	0.11
chronic kidney disease	21.9; 118/539	29.7; 30/101	0.10
COPD	12.6; 68/539	11.0; 11/100	0.74
current smoking	56.1; 291/519	61.2; 60/98	0.38
previous pharmacotherapy			
diuretics	61.2; 314/513	70.5%; 67/95	0.11
furosemide/torasemide dose, mg[a]	31.5 ±42.7; n = 452	54.8 ±81.1; n = 81	0.03
aldosterone antagonists	38.8; 198/510	56.4; 53/94	0.002
ACEIs	62.2; 317/510	60.6; 57/94	0.82
ARBs	8.1; 41/507	7.5; 7/94	1.00
β-blockers	71.2; 363/510	75.5; 71/94	0.45
antiarrhythmic drugs[b]	7.9; 40/509	10.9; 10/92	0.31
statins	52.6; 269/511	55.3; 52/94	0.65
clinical status on admission			
cardiogenic shock	2.9; 14/482	2.1%; 2/100	1.00
NYHA class	3 (2–3); n = 536	3 (3–4); n = 101	0.02
SBP, mmHg	134 (120–150); n = 537	120 (100–140); n = 101	<0.0001
DBP, mmHg	80 (70–90); n = 537	70 (60–80); n = 101	<0.0001
heart rate, bpm	80 (70–100); n = 537	80 (70–96); n = 101	0.29
atrial fibrillation	18.4; 99/538	10.9; 11/101	0.08
VF or VT as a cause of admission	4.1; 22/537	7.9; 8/101	0.12
ACS as a cause of admission	30.9; 166/537	25.7; 26/101	0.35
laboratory findings on admission			
serum sodium, mmol/l	139.0 (137.0–141.0); n = 540	133.0 (131.7–134.0); n = 101	<0.0001
serum potassium, mmol/l	4.4 (4.0–4.7); n = 539	4.4 (4.0–7.9); n = 101	0.96
serum creatinine, mg/dl	1.09 (0.90–1.37); n = 520	1.17 (0.95–1.64); n = 98	0.02
hemoglobin, g/dl	13.3 (12.1–14.7); n = 533	13.0 (11.6–14.1); n = 100	0.04
major management during index hospitalization, clinical status and laboratory findings at discharge			
PCI/CABG during hospitalization	13.5; 73/540	12.9; 13/101	1.00
ICD implantation during hospitalization	6.1; 33/540	4.9; 5/101	0.82
SBP at discharge, mmHg	120 (110–130); n = 521	110 (100–120); n = 89	<0.0001
serum creatinine at discharge, mg/dl	1.10 (0.90–1.40); n = 359	1.15 (0.92–1.53); n = 73	0.42

TABLE 1 Baseline characteristics, clinical course of index hospitalization, and in-hospital and long-term outcomes of patients with and without hyponatremia at hospital admission

Characteristics	Serum sodium level on admission (n = 641)		*P* value
	normonatremia (n = 540)	hyponatremia (n = 101)	
pharmacotherapy at hospital discharge[c]			
diuretics	80.3; 424/528	79.1; 72/91	0.78
aldosterone antagonists	64.3; 339/527	56.0; 51/91	0.16
ACEIs	72.5; 383/528	72.5; 66/91	1.00
ARBs	7.9; 42/526	13.2; 12/91	0.11
β-blockers	86.6; 458/529	87.9; 80/91	0.87
antiarrhythmic drugs[b]	10.4; 55/529	7.7; 8/91	0.57
statins	68.8; 364/529	69.2; 63/91	1.00
in-hospital outcome			
length of hospital stay, d	7 (4–10); n = 540	9 (6–16); n = 101	<0.0001
death during hospitalization	1.9; 10/540	9.9%; 10/101	<0.0001
1-year outcome			
death	10.4; 56/540	31.7%; 32/101	<0.0001
death or rehospitalization	35.9; 152/423	56.5%; 48/85	<0.0001

In each bar, a total number of patients for whom a given variable was available in the registry is shown. Continuous and ordinal variables are shown as a median (interquartile range) or mean ± standard deviation. *P* values are given for the differences between the groups.

a torasemide doses were converted to equivalent furosemide doses
b except for amiodarone use, no data on the classes or exact preparations of antiarrhythmic drugs were available; there was no difference in the frequency of amiodarone use between the groups
c in patients who survived to hospital discharge

Conversion factors to SI units are as follows: for creatinine, 88.4; for hemoglobin, 0.6206.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; HFPEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia

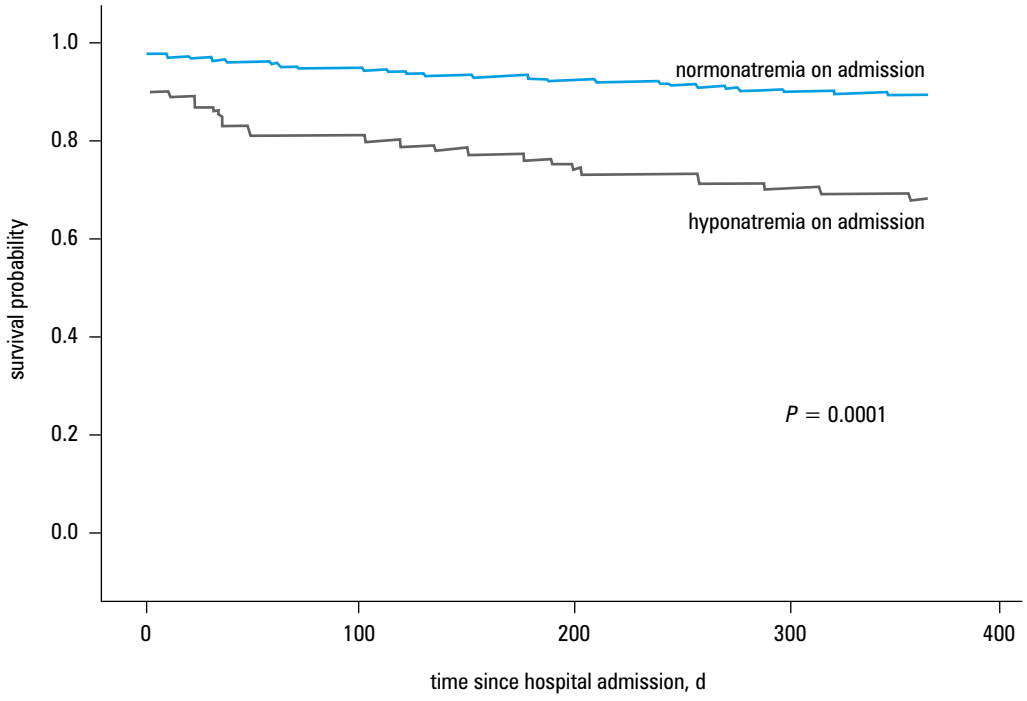


FIGURE 2 Kaplan–Meier curves for the primary endpoint in hyponatremic and normonatremic patients

number at risk

normonatremia	540	523	518	512	508	505	502	499	497	487	486	484
hyponatremia	101	88	82	80	79	77	74	74	72	71	70	69

TABLE 2 Predictors of the primary and secondary endpoints at 1 year (univariate analysis)

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
demographic data				
age, per 10-year increase	1.45 (1.20–1.75)	0.0001	1.09 (0.98–1.22)	0.10
male sex, yes vs no	0.79 (0.52–1.21)	0.27	1.01 (0.75–1.35)	0.97
BMI, per 1-kg/m^2 increase	0.96 (0.91–1.01)	0.09	1.00 (0.97–1.03)	0.87
heart failure				
LVEF, per 5% increase	0.92 (0.84–1.003)	0.059	0.93 (0.88–0.98)	0.006
previous HF hospitalization, yes vs no	0.92 (0.60–1.40)	0.69	1.28 (0.96–1.71)	0.09
medical history				
hypertension, yes vs no	1.32 (0.83–2.09)	0.25	0.85 (0.64–1.14)	0.27
coronary artery disease, yes vs no	1.60 (1.02–2.52)	0.04	1.35 (1.01–1.79)	0.04
prior PCI or CABG, yes vs no	1.24 (0.80–1.90)	0.34	1.47 (1.11–1.95)	0.008
history of atrial fibrillation, yes vs no	1.56 (1.03–2.37)	0.04	1.32 (1.00–1.74)	0.052
peripheral artery disease, yes vs no	1.17 (0.59–2.33)	0.66	1.22 (0.77–1.93)	0.41
diabetes, yes vs no	1.60 (1.05–2.43)	0.03	1.37 (1.03–1.81)	0.03
depression, yes vs no	0.81 (0.20–3.29)	0.77	0.87 (0.36–2.11)	0.75
COPD, yes vs no	0.91 (0.47–1.76)	0.78	0.97 (0.64–1.49)	0.90
current smoking, yes vs no	0.89 (0.58–1.37)	0.58	0.97 (0.73–1.30)	0.85
previous pharmacotherapy				
diuretics, yes vs no	1.45 (0.90–2.34)	0.13	1.90 (1.38–2.62)	<0.0001
aldosterone antagonists, yes vs no	1.37 (0.88–2.12)	0.16	1.39 (1.04–1.85)	0.03
ACEIs, yes vs no	1.03 (0.66–1.63)	0.89	1.17 (0.87–1.58)	0.31
ARBs, yes vs no	1.09 (0.50–2.37)	0.83	1.08 (0.66–1.75)	0.76
β-blockers, yes vs no	0.97 (0.60–1.57)	0.90	1.25 (0.89–1.74)	0.20
antiarrhythmic drugs, yes vs no	0.92 (0.40–2.13)	0.85	0.99 (0.58–1.71)	0.98
statins, yes vs no	0.84 (0.54–1.31)	0.45	1.20 (0.90–1.60)	0.22
clinical status on admission				
cardiogenic shock, yes vs no	2.07 (0.76–5.66)	0.16	1.83 (0.86–3.90)	0.12
NYHA class, per 1-class increase	1.87 (1.38–2.54)	<0.0001	1.51 (1.24–1.83)	<0.0001
SBP, per 10-mmHg increase	0.89 (0.82–0.96)	0.006	0.90 (0.86–0.95)	0.0001
heart rate, per 10-bpm increase	1.14 (1.06–1.24)	0.001	1.05 (0.99–1.11)	0.13
atrial fibrillation, yes vs no	1.28 (0.76–2.15)	0.35	1.26 (0.87–1.81)	0.22
VF or VT as a cause of admission, yes vs no	1.22 (0.49–3.00)	0.67	0.92 (0.46–1.87)	0.83
ACS as a cause of admission, yes vs no	1.29 (0.83–2.00)	0.26	1.09 (0.80–1.47)	0.59
laboratory findings on admission				
hyponatremia, yes vs no	3.49 (2.26–5.40)	<0.0001	1.97 (1.42–2.72)	<0.0001
serum potassium concentration, per 0.5-mmol/l increase	1.07 (0.90–1.27)	0.46	0.96 (0.85–1.08)	0.45
serum creatinine concentration, per 1-mg/dl increase	1.01 (0.96–1.06)	0.77	1.25 (1.07–1.46)	0.006
hemoglobin, per 1-g/dl increase	0.88 (0.80–0.98)	0.02	0.89 (0.83–0.96)	0.002
major management during index hospitalization				
PCI/CABG during hospitalization, yes vs no	1.02 (0.56–1.88)	0.95	1.06 (0.71–1.59)	0.78
ICD implantation during hospitalization, yes vs no	0.95 (0.39–2.34)	0.91	0.94 (0.53–1.69)	0.84

For conversion factors to SI units: see TABLE 1

Abbreviations: CI, confidence interval; HR, hazard ratio; others, see TABLE 1

TABLE 3 Predictors of death at 1 year (multivariate analysis)

	HR (95% CI)	*P* value
age, per 10-year increase	1.03 (1.01–1.05)	0.008
coronary artery disease, yes vs no	1.38 (0.87–2.21)	0.18
history of atrial fibrillation, yes vs no	1.32 (0.85–2.05)	0.22
diabetes, yes vs no	1.44 (0.93–2.21)	0.10
NYHA class on admission, per 1-class increase	1.65 (1.19–2.28)	0.003
SBP on admission, per 10-mmHg increase	0.99 (0.98–1.00)	0.09
heart rate on admission, per 10-bpm increase	1.011 (1.003–1.019)	0.01
hyponatremia on admission, yes vs no	3.07 (1.94–4.87)	<0.0001
hemoglobin on admission, per 1-g/dl increase	0.99 (0.88–1.10)	0.79

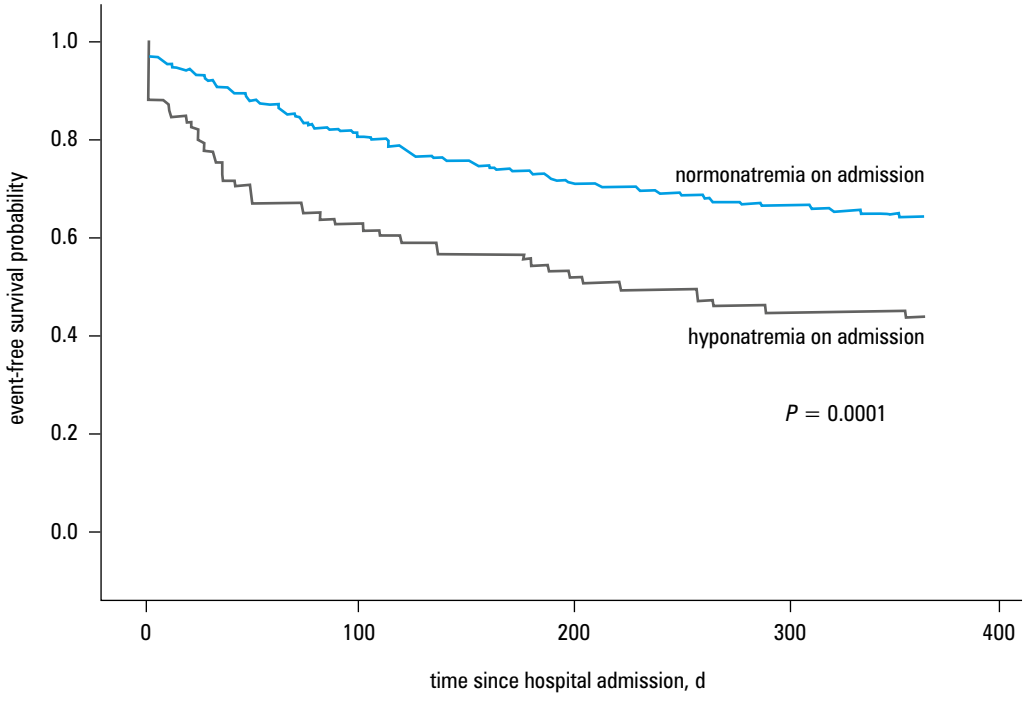
For conversion factors to SI units: see TABLE 1

Abbreviations: see TABLES 1 and 2

secondary endpoint analysis. The secondary endpoint occurred in 200 of 508 patients (39.4%), including 48 of 85 hyponatremic patients (56.5%) and 152 of 423 normonatremic patients (35.9%; *P* <0.0001), as shown in TABLE 1. One-year event-free survival probability of both patient groups is demonstrated in FIGURE 3. Hyponatremia was found to be predictive of the secondary endpoint in both univariate and multivariate Cox proportional hazards regression models (TABLES 2 and 4). Owing to the lack of complete data for some of the patients in the registry, the multivariate analysis included only those patients for whom all the required parameters were available (392 of 508 [77.2%]; 61.2% of the whole study group).

One-year outcome in patients who survived to hospital discharge (subgroup analysis) As shown in TABLE 1, of 641 patients included in the study, 20 patients died during index hospitalization, leaving a subgroup of 621 patients (530 normo- and 91 hyponatremic patients) for the additional analysis of long-term outcomes. Forty-six of 530 normonatremic patients (8.7%) and 22 of 91 hyponatremic patients (24.2%) died during the 1-year follow-up (*P* <0.0001). Hyponatremia was predictive of the primary endpoint in the univariate analysis (hazard ratio [HR], 2.88; 95% confidence interval [CI], 1.72–4.83; *P* <0.0001) and remained an independent risk factor for death at 1 year in the multivariate model (HR, 2.11; 95% CI, 1.15–3.86; *P* = 0.02). Other variables found to be predictive of the primary endpoint in the univariate analyses and, consequently, included in the multivariate model were age, BMI, a history of coronary artery disease, previous coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), heart rate on admission, SBP at discharge, and treatment with ACEIs at discharge).

As shown in FIGURE 1, data on hospital readmissions at 1 year were missing for 133 patients, leaving 488 successfully discharged patients (413 normonatremic and 75 hyponatremic patients) for the secondary endpoint analysis. The secondary endpoint was reached by 142 of 413 normonatremic patients (34.4%) and 38 of 75 hyponatremic patients (50.7%) (*P* = 0.009). In the univariate analysis, hyponatremia was predictive



number at risk													
normonatremia	423	390	368	347	332	320	310	300	293	258	282	276	271
hyponatremia	85	66	57	53	50	48	47	43	42	39	38	38	37

FIGURE 3 Kaplan–Meier curves for the secondary endpoint in hyponatremic and normonatremic patients

TABLE 4 Predictors of death or rehospitalization for heart failure at 1 year (multivariate analysis)

	HR (95% CI)	*P* value
LVEF, per 5% increase	0.99 (0.98–1.00)	0.19
coronary artery disease, yes vs no	0.97 (0.65–1.44)	0.87
prior PCI or CABG, yes vs no	1.42 (0.96–2.12)	0.08
diabetes, yes vs no	1.26 (0.90–1.78)	0.18
prior diuretic treatment, yes vs no	1.25 (0.84–1.87)	0.27
prior aldosterone antagonist treatment, yes vs no	1.06 (0.73–1.53)	0.77
NYHA class on admission, per 1-class increase	1.32 (1.04–1.68)	0.02
SBP on admission, per 10-mmHg increase	0.99 (0.99–1.00)	0.07
hyponatremia on admission, yes vs no	1.71 (1.16–2.52)	0.007
serum creatinine on admission, per 1-mg/dl increase	1.13 (0.92–1.40)	0.25
hemoglobin on admission, per 1-g/dl increase	0.96 (0.88–1.05)	0.39

For conversion factors to SI units: see TABLE 1

Abbreviations: see TABLES 1 and 2

of the secondary endpoint (HR, 1.73; 95% CI, 1.21–2.47; $P = 0.003$). There was a borderline significance for hyponatremia as a predictor of the secondary endpoint in the multivariate analysis (HR, 1.51; 95% CI, 0.99–2.29; $P = 0.054$). Other variables found to be predictive of the secondary endpoint in the univariate analyses and, consequently, included in the multivariate model were LVEF, a history of previous hospitalization for HF, previous coronary revascularization (PCI or CABG), NYHA class on admission, SBP on admission, serum creatinine on admission, hemoglobin on admission, and SBP at discharge.

DISCUSSION Hyponatremia is one of the most common electrolyte abnormalities in HF patients, with a prevalence ranging from 10% to 54%.[2-6,8-11,13,20,21] However, severe hyponatremia, with a serum sodium concentration of less than 130 mmol/l, is rare, with the prevalence reported as 4% to 5% of patients with acute decompensated HF.[15,22] In our analysis, we observed hyponatremia in 15.8% and severe hyponatremia in 2.2% of the patients.

Hyponatremia in HF is believed to be primarily caused by a low cardiac output resulting in augmented secretion of arginine vasopressin (AVP). High concentrations of AVP were reported in patients with HF, with their progressive increase with worsening of HF symptoms.[23] Interestingly, AVP secretion has been recently reported to be higher in normonatremic patients with chronic HF than in patients with the syndrome of inappropriate antidiuretic hormone (SIADH), with the highest AVP secretion observed in hyponatremic HF patients.[24] Under physiological conditions, the main stimulus for AVP release from the posterior pituitary gland is increased plasma osmolality, while nonosmotic triggering factors, including hypovolemia and activation of angiotensin II receptors, play a less prominent role.[25] In HF patients, the regulation of AVP secretion becomes less dependent on plasma osmolality.[23,26] Low cardiac output due to left ventricular dysfunction leads to reduced systemic arterial blood pressure, which is interpreted as hypovolemia, even in patients with coexisting fluid retention and volume overload.[1,23,25] These assumptions have been recently confirmed by Imamura et al.[27] In a group of 162 patients with advanced HF, the plasma AVP level was inversely correlated with both the serum sodium concentration and cardiac index. In comparison with those patients, a significantly higher cardiac index, lower plasma AVP level, and higher serum sodium concentration were observed in 80 patients at 3 months after left ventricular assist device (LVAD) implantation or heart transplantation. Interestingly, in patients after LVAD implantation or heart transplantation, the plasma AVP concentration was found to correlate positively with the serum sodium concentration and not to correlate with the cardiac index. These findings demonstrate that in HF patients, AVP release, triggered by reduced cardiac output, is not inhibited by decreased plasma osmolality. They also imply that an improvement in cardiac function might restore the regulation of AVP secretion, so that AVP release would be again induced predominantly by hyperosmolality (eg, due to an increase in the serum sodium concentration).

The pathomechanism of AVP secretion in response to a reduced cardiac output probably involves an excessive activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, both observed in HF.[25] Hyponatremia was associated with higher plasma renin activity as well as with higher aldosterone and norepinephrine concentrations.[28] The activation of angiotensin II receptors in the posterior pituitary gland triggers AVP release and, in the hypothalamus, it stimulates the thirst center leading to increased water intake. Some evidence indicates that treatment with ACEIs might be beneficial in hyponatremic patients.[25] On the other hand, single case reports of ACEI-induced hyponatremia, which could be attributed to SIADH, are available in the published literature.[29,30] In our study, no difference in the frequency of ACEI use was observed between hypo- and normonatremic patients.

Interestingly, despite the described association of hyponatremia with the reduced cardiac output and low SBP, there was no relationship between the serum sodium concentration and LVEF either in our analysis or in most of the available studies.[4,5,11,13] Such an association was observed in the OPTIMZE-HF registry but the analysis included as many as 48 612 patients and although the difference in LVEF between hyponatremic and normonatremic patients was significant, it was quite modest (38.5% vs 39.1%).[10] Hyponatremia is also highly prevalent in patients with HF with preserved LVEF.[21,31] In our study, we did not observe any difference in the prevalence of hyponatremia between patients with reduced LVEF and those with preserved LVEF. The etiology of hyponatremia in patients with HF with preserved

LVEF may involve a reduced stroke volume due to decreased diastolic filling as well as the influence of diuretic treatment.

Hyponatremia in HF may be a consequence of intensive diuretic therapy.[1,3,11,25] In our study, hyponatremic patients were significantly more often treated with aldosterone antagonists and somewhat more commonly treated with loop diuretics. In addition, they received significantly higher doses of loop diuretics prior to the index hospitalization. Given the fact that hyponatremia was demonstrated to be a prognostic factor in HF patients, it seems prudent to advise caution in using loop diuretics and to encourage dose reduction or complete drug discontinuation whenever possible, especially in patients with already coexisting hyponatremia or at risk of its development. However, this cannot be recommended for aldosterone antagonists, as both spironolactone and eplerenone were shown to improve prognosis of HF patients. Our study showed no significant difference in pharmacotherapy administered at discharge between hyponatremic and normonatremic patients, that is, hyponatremic patients were prescribed loop diuretics as often as normonatremic patients, and the overall frequency of diuretic treatment was higher at hospital discharge compared with hospital admission.

In HF patients, iatrogenic hyponatremia can be also triggered by the use of antiarrhythmic drugs.[4] The initiation of treatment with flecainide, a class Ic agent, whose antiarrhythmic mechanism of action is based on the blockade of sodium channels, was reported to induce a 10-mmol/l decrease in sodium concentrations in 9% of 663 patients.[32] Furthermore, case reports of SIADH in the course of amiodarone therapy have been published.[33,34] However, in our study, we did not observe any association between hyponatremia and the use of antiarrhythmic treatment, although it should be stressed that we lacked data on the classes and exact preparations of antiarrhythmic drugs used by patients in the ESC-HF Pilot study.

In our study, hyponatremic patients were characterized by a worse clinical status at hospital admission, including a higher NYHA class and lower systolic and diastolic blood pressure values, as well as by higher serum creatinine and lower hemoglobin concentrations. It seems advisable that such clinical profile should prompt careful analysis of electrolyte disturbances and, despite more pronounced congestive symptoms (as depicted by the higher NYHA class), warrant caution with diuretic treatment, especially given the possibility of hypotension and renal dysfunction in these patients. The observed association of hyponatremia with lower SBP seems to be bidirectional: low SBP due to reduced cardiac output may result in increased AVP secretion and dilutional (hypervolemic) hyponatremia, while hyponatremia itself (aggravated by diuretic therapy) might lead to hypotension.[10,11]

In hospitalized HF patients, hyponatremia has been previously associated with unfavorable clinical course and in-hospital outcome including more frequent deterioration of renal function during hospitalization, more frequent need for dialysis, intravenous inotropic support, LVAD and mechanical ventilatory support, longer hospital stay, and higher in-hospital mortality.[2-5,7,10,11,13] In the current analysis, hyponatremic patients were hospitalized longer and were at a higher risk of death during the index hospitalization compared with normonatremic patients. In our previous study conducted in Polish ESC-HF Pilot participants, a lower sodium concentration on admission proved to be an independent predictive factor of death during hospitalization.[18]

In our current study conducted in patients hospitalized for HF, hyponatremia at hospital admission was an independent predictor of all-cause death at 1 year as well as death or readmission for HF worsening during 1-year follow-up. Furthermore, hyponatremia on admission proved predictive of long-term mortality even in the subgroup of patients who survived to hospital discharge. Hyponatremia has been previously reported to be predictive of mortality and morbidity after discharge in patients hospitalized for decompensated HF.[2,8-11,13,14] However, most of these studies either included serum sodium concentration merely as one of many variables and did not specifically focus on clinical characteristics and prognosis of hyponatremic HF patients compared with normonatremic individuals or assessed only early outcomes (ie, up to 6 months after the index hospitalization).[8,10,11,13,14] Thus far, only 2 studies were specifically designed to assess clinical characteristics and long-term outcomes (ie, 1-year or longer) of hyponatremic patients hospitalized for decompensated HF.[2,9] In both of these studies, multivariate analyses evaluating the effect of hyponatremia at hospital admission on long-term survival were adjusted only for baseline variables, neglecting the possible effect of proven prognostic factors, such as clinical status at discharge or discharge pharmacotherapy (in particular the use of β-blockers and ACEIs) on long-term prognosis in HF patients.[2,9] Contrary to those studies, our subgroup analysis focused on patients successfully discharged after hospitalization for HF, thereby including variables other than merely the baseline variables (eg, pharmacotherapy at discharge and SBP at discharge) and avoiding artificial overestimation of the effect of hyponatremia on long-term survival by excluding patients who died during hospitalization (given the fact that hyponatremic patients were at a significantly higher risk of in-hospital death, as proven in our previous analysis).[18]

Hyponatremia was also found to be a prognostic factor in ambulatory HF patients.[20,21,35] A recent meta-analysis of 22 studies, including a total of 14 766 patients with HF, has demonstrated that in a 3-year follow-up, hyponatremia was an independent predictor of all-cause death in both

HF with reduced LVEF and HF with preserved LVEF. The risk of death increased linearly with serum sodium levels lower than 140 mmol/l.[36]

So far, it is unclear whether hyponatremia itself deteriorates the clinical course of HF or whether it merely acts as a marker of neurohormonal activation reflecting HF severity.[1,25] Despite a proven association of hyponatremia with HF prognosis, no consistent evidence exists that amelioration of hyponatremia during hospitalization for HF results in reduced mortality.[11,13,37,38] Furthermore, in the EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), therapy with tolvaptan, an AVP type 2 receptor antagonist, did not improve survival in patients hospitalized for HF.[38] This might be partly explained by the fact that an increase in the serum AVP concentration, observed during tolvaptan therapy, might have deleterious effects on the cardiovascular system via excessive activation of type 1 AVP receptors.[1,39] In patients with HF, increased plasma AVP concentration was associated with reduced survival.[27] Results from a post hoc analysis of the EVEREST study implicate that treatment with tolvaptan might be favorable in HF patients with coexisting severe hyponatremia.[40]

Based solely on the results of our study, we cannot conclude whether hyponatremia itself influences survival in HF patients and whether an increase in the sodium concentration would benefit hyponatremic HF patients. Thus, we cannot unequivocally recommend any therapeutical approach focused primarily on the amelioration of hyponatremia. However, patients with hyponatremia at hospital admission are at a higher risk of death even after successful hospital discharge, and thus, a careful ambulatory follow-up of such patients, including more cautious diuretic treatment, seems justified. The findings of our study seem particularly important in the context of increasing mortality observed in Polish HF patients in recent years.[41]

Limitations of the study The limitations of our study arise from the type of data we analyzed. In contrast to randomized clinical trials, the advantage of registries is that they include "real-world" patients. However, there are also some important drawbacks of registries, such as their observational character and incompleteness of the data. In the present study, data on hospital readmissions at 1 year were missing for 133 of 641 patients (20.8%), leaving 508 patients for the secondary endpoint analysis. Furthermore, owing to the incompleteness of the data for some of the variables included in the Cox proportional hazards regression model, the multivariate model of the predictors of the secondary endpoint included only 392 of those 508 patients (61.2% of the whole study group).

Our choice of variables included into the univariate analysis was motivated by the results of previous large-scale registries.[19] However, some of the factors previously reported to be predictive of the postdischarge outcome of hospitalized HF patients were not available in the ESC-HF Pilot database (eg, a history of liver disease) or contained missing data for a substantial number (ie, ≥15%) of patients (eg, serum creatinine concentration at hospital discharge) and thus, were not included in the Cox proportional hazards regression models.[19]

The ESC-HF Pilot encompassed a broad spectrum of HF patients, including both patients with reduced LVEF and patients with preserved LVEF. It could be hypothesized that, given the pathophysiological relationship between hyponatremia and reduced cardiac output, including patients with HF and preserved LVEF might have obscured the results of our study. However, the prevalence of hyponatremia in patients with HF with preserved LVEF has been previously reported to be similar to that observed in patients with HF with reduced LVEF.[10,11,21,31] In our study, the prevalence of hyponatremia was the same in patients with preserved LVEF as in patients with reduced LVEF. Thus, we assume that including patients with HF with preserved LVEF did not affect the results of our study in a significant way.

Conclusions Hyponatremia is a common laboratory finding in patients admitted to the hospital for HF. Even in patients who survive to hospital discharge, hyponatremia on admission remains an independent predictive factor of all-cause mortality in long-term follow-up.

Contribution statement AKC designed the analysis, researched data, conducted data interpretation, and wrote the manuscript. KO, PB, AT, MG, MW, and MM researched data. MP performed statistical analysis. JD and GO designed the study. JD coordinated the survey nationwide. All authors reviewed the manuscript and approved its final version.

Acknowledgments All analyses were conducted based on the data from the Polish part of the ESC-HF Pilot, coordinated nationwide by Professor Jarosław Drożdż (TABLE 5).

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ARTYKUŁ ORYGINALNY

Charakterystyka kliniczna i rokowanie roczne pacjentów z hiponatremią hospitalizowanych z powodu niewydolności serca

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hiponatremia, hospitalizacja, niewydolność serca, rokowanie, sód

STRESZCZENIE

WPROWADZENIE W dotychczasowych badaniach wykazano, że u chorych z niewydolnością serca (NS) hiponatremia jest niekorzystnym czynnikiem prognostycznym. Jednak niewiele prac miało na celu ocenę wpływu hiponatremii na rokowanie długoterminowe u pacjentów hospitalizowanych z powodu NS.

CELE Celem badania była ocena charakterystyki klinicznej i rokowania rocznego pacjentów hospitalizowanych z powodu NS, u których przy przyjęciu do szpitala stwierdzono hiponatremię.

PACJENCI I METODY Do analizy włączono 641 polskich uczestników Pilotażowego Rejestru NS Europejskiego Towarzystwa Kardiologicznego. Pierwotny punkt końcowy stanowiła śmiertelność całkowita po roku od hospitalizacji. Wtórny punkt końcowy obejmował zgon z jakiejkolwiek przyczyny i ponowną hospitalizację z powodu zaostrzenia objawów NS w trakcie rocznej obserwacji.

WYNIKI Hiponatremię stwierdzono u 15,8% spośród 641 pacjentów. Chorzy z hiponatremią charakteryzowali się wyższą klasą czynnościową NYHA, niższymi wartościami ciśnienia tętniczego, niższym wskaźnikiem masy ciała, wyższym stężeniem kreatyniny i niższym stężeniem hemoglobiny przy przyjęciu do szpitala. W porównaniu z pacjentami normonatremicznymi, u chorych z hiponatremią stwierdzono wyższe ryzyko: zgonu w trakcie hospitalizacji (1,9% *vs* 9,9%; p <0,0001), zgonu po roku obserwacji (10,4% *vs* 31,7%; p <0,0001) oraz zgonu lub ponownej hospitalizacji po roku (35,9% *vs* 56,5%; p <0.0001). W analizach wieloczynnikowych hiponatremia okazała się niezależnym predyktorem wystąpienia pierwotnego (HR 3,07; 95% CI 1,94–4,87; p <0,0001) i drugorzędowego punktu końcowego (HR 1,71; 95% CI 1,16–2,52; p = 0,007). Hiponatremia była niezależnym predyktorem pierwotnego punktu końcowego także w podgrupie 621 pacjentów, którzy przeżyli hospitalizację (HR 2,11; 95% CI 1,15–3,86; p = 0,02).

WNIOSKI Hiponatremia często występuje u pacjentów hospitalizowanych z powodu NS. Nawet u chorych, którzy przeżywają do wypisu ze szpitala, hiponatremia stwierdzona przy przyjęciu pozostaje niezależnym predyktorem zgonu w obserwacji odległej.

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