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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Clinical characteristics and predictors of one-year outcome of heart failure patients with atrial fibrillation compared to heart failure patients in sinus rhythm

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Abstract

Background: Atrial fibrillation (AF) frequently coexists with heart failure (HF).

Aim: To assess clinical characteristics and to identify predictors of one-year outcome of patients hospitalised for HF, depending on whether they were in sinus rhythm (SR) or had AF.

Methods: The study included Polish patients hospitalised for HF, participating in the Heart Failure Pilot Survey of the European Society of Cardiology, who were followed for 12 months after discharge. Patients with paced heart rhythm were excluded from the study. The primary endpoint was all-cause death at 12 months.

Results: The final analysis included 587 patients. AF occurred in 215 (36.6%) patients. Compared to patients in SR, patients with AF were older, more often had a history of previous HF hospitalisation, were characterised by a higher New York Heart Association (NYHA) class, higher heart rate, and lower diastolic blood pressure at hospital admission, and had higher serum creatinine and lower haemoglobin concentration at admission. In-hospital mortality was higher in AF patients compared to SR patients (5.1% vs. 2.4%, respectively), but the difference did not reach statistical significance ($p = 0.1$). The primary endpoint occurred in 41 of 215 AF patients (19.1%) and in 40 of 372 SR patients (10.8%; $p = 0.006$). In a multivariate analysis, predictors of the primary endpoint in AF patients were: higher NYHA class at hospital admission ($p = 0.02$), higher admission heart rate ($p = 0.04$), lower admission serum sodium concentration ($p = 0.0001$), and higher heart rate at discharge ($p = 0.01$). In patients with SR, independent predictors of the primary endpoint included: older age ($p = 0.007$), lower serum sodium concentration at admission ($p = 0.0006$), and higher heart rate at discharge ($p = 0.008$).

Conclusions: Patients with HF and concomitant AF differ significantly from HF patients in SR. In the studied group of real-world HF patients, serum sodium concentration at hospital admission and heart rate at hospital discharge were independent prognostic factors in patients with AF and in patients in SR. In contrast to SR patients, heart rate at hospital admission in AF patients was also predictive of long-term mortality.

Key words: atrial fibrillation, sinus rhythm, heart failure, hospitalisation, prognosis

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INTRODUCTION

Atrial fibrillation (AF) is a frequent comorbidity in patients with heart failure (HF) [1]. Over six million Europeans suffer from AF, and it is expected that its prevalence will at least double over the next 20 years [2]. Despite improved medical therapy, more than 50% of patients hospitalised for HF and 40% of patients hospitalised for AF are readmitted to hospital within 6–12 months and remain an important driver of health-care costs [3–5]. Coexistence of HF and AF further increases the cost of medical care. Cost analyses demonstrated that in-hospital expenditures in HF patients with AF are several times higher than in HF patients with sinus rhythm (SR), which is associated with longer hospital stay, greater stroke severity, and higher in-hospital mortality [2, 3]. AF in HF also predicts more frequent HF rehospitalisation [6–8]. Patients with coexisting HF and AF are at higher risk of thromboembolic events than patients with HF alone [9, 10]. A recently published meta-analysis indicates that, in contrast to SR–HF patients, beta-blockers do not improve prognosis in AF–HF patients [11]. These data suggest that AF patients constitute a particular subgroup within the HF population and confirm the need for further comparative studies of AF–HF patients and SR–HF patients. Of particular importance are data obtained from registries, which reflect real-life patient populations. The Heart Failure Pilot Survey of the European Society of Cardiology (ESC-HF Pilot) was a prospective, multicentre registry of HF patients across Europe [12].

The aim of this study was to evaluate the prevalence of AF in Polish patients hospitalised for HF, to assess clinical characteristics of these patients in comparison to SR–HF patients, and to identify predictors of mortality and rehospitalisation in one-year observation in both of these groups.

METHODS

Study population

The ESC-HF Pilot was a prospective, multicentre, observational survey of HF patients presenting to 136 European cardiology centres, including 29 centres from Poland [12]. The survey was conducted from October 2009 to May 2010, and included outpatients with chronic HF, as well as patients admitted to hospital for acute HF (new-onset or worsening HF). The study enrolled patients who met diagnostic criteria for HF and were over 18 years of age. There were no specific exclusion criteria.

Researchers gathered data regarding clinical presentation, diagnostic tests results, demographics, medical history, previous and current treatment, clinical course of index hospitalisation (in case of inpatients), as well as one-year follow-up. All patients provided informed written consent. Approval for the study was obtained from the local Ethical Review Board.

The current analysis involved Polish ESC-HF Pilot patients hospitalised for HF. The study excluded outpatients seen in ambulatory care. All patients with available electrocardiographic (ECG) documentation on heart rhythm (12-lead ECG or 24-h Holter monitoring) during index hospitalisation were included in the analysis. Patients with paced heart rhythm were excluded from the study for two reasons: 1) ESC-HF Pilot case report forms enabled investigators to choose only one (leading) heart rhythm for each patient's admission ECG: SR, AF, paced rhythm, or "other", which precluded reliable discrimination between patients with paced rhythm and underlying AF and patients with paced rhythm without AF; and 2) we assumed that the rhythm pacing might influence other variables (such as heart rate or the frequency of beta-blockers use) that we planned to compare between the AF and SR groups.

Study groups

Patients were assigned to the "AF group" based on previous documentation and ECG performed during index hospitalisation. The "AF group" included patients with AF, regardless of AF type (paroxysmal, persistent, or permanent). "AF patients" did not need to be in AF at hospital admission. Patients were assigned to the "SR group" provided that their basic rhythm was SR and that there was no evidence for AF either in previous medical documentation or in ECGs or Holter monitoring performed during index hospitalisation.

Comparative analysis of patients with AF and patients in SR

Atrial fibrillation and SR patients were compared with regard to baseline characteristics (demographic data, medical history, and previous medication), clinical status at hospital admission and at hospital discharge, laboratory findings at admission, major therapeutic procedures during index hospitalisation, and discharge pharmacotherapy, as well as in-hospital (all-cause death during index hospitalisation and length of hospital stay) and one-year outcome (all-cause death and all-cause death or rehospitalisation for decompensated HF).

Clinical endpoints at one-year follow-up

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

The main goal of the study was to compare predictors of the primary and the secondary endpoint between the AF and SR groups. Additionally, we sought to determine whether AF was an independent prognostic factor in the whole studied HF population.

Statistical analysis

Categorical data were presented as number of patients and percentages. Normally distributed continuous variables were presented as mean value and standard deviation. For ordinal variables and non-normally distributed continuous variables the median value and interquartile range were used. To determine differences between groups, Fisher's exact test

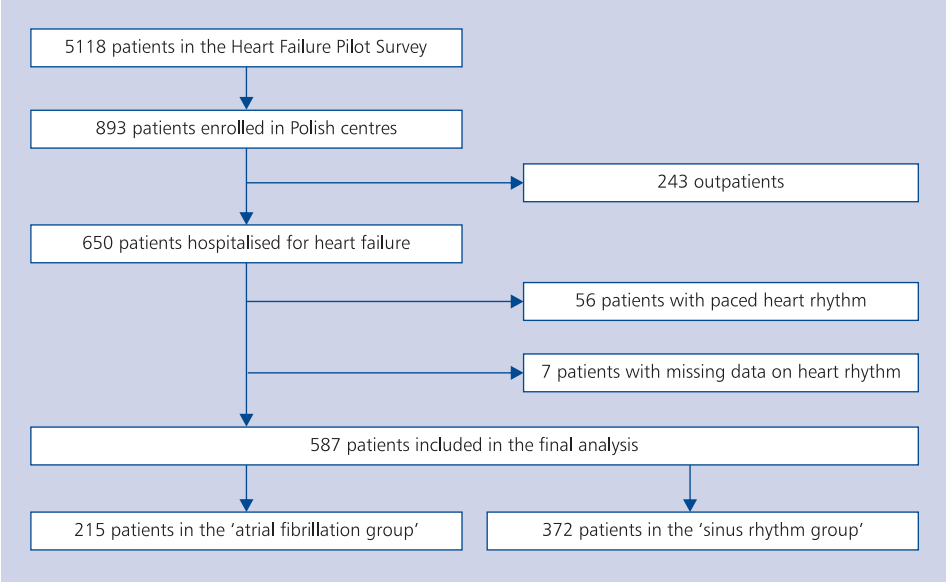

Figure 1. Flow chart of patient enrolment in the current analysis

was performed for categorical variables and Mann-Whitney U test for continuous and ordinal variables. Kaplan-Meier curves were developed for the primary and the secondary endpoint in the two groups. Cox proportional hazards regression model was used to identify predictors of the primary and the secondary endpoint. Variables found to be statistically significant in univariate analyses were included into multivariate analyses. Due to the relatively small size of the study groups, in order to maintain adequate events per predictor variable value, pharmacotherapy was not included in the Cox proportional hazards regression model. Statistical significance was considered for p-values lower than 0.05 for all tests. All tests were two-tailed. Statistical analyses were performed using SAS software, version 9.2.

RESULTS

Study group selection

A total of 5118 patients were enrolled in the ESC-HF Pilot across Europe. In the Polish cohort of the registry there were 893 patients, including 650 inpatients. Seven patients with missing ECG documentation and 56 patients with paced heart rhythm were excluded from the study, leaving 587 patients for the final analysis. Data on one-year survival were available for all 587 patients. Data on rehospitalisations for decompensated HF were missing for 128 patients, leaving 459 patients (78.2% of 587 patients) for the secondary endpoint analysis. Figure 1 shows the flow chart of patient enrolment in the study.

Clinical characteristics of patients with AF

Atrial fibrillation was found in 215 (36.6%) of 587 patients. Out of those 215 patients, 203 (94.4%) patients had a previous diagnosis of AF (54 [26.6%] patients of paroxysmal, 33 [16.3%] patients of persistent, and 116 [57.1%] patients of permanent AF). One hundred and fifty-two (71%) patients had AF at hospital admission, and in 89 (41.4%) patients AF was considered the reason of HF decompensation leading to index hospitalisation.

Out of the 63 remaining Polish inpatients excluded from the study due to paced heart rhythm (56 patients) or missing ECG documentation (7 patients), 28 had a previous history of AF. Thus, the overall prevalence of AF in the whole population of Polish ESC-HF Pilot patients hospitalised for HF may be estimated at 37.4% (243 out of 650 Polish inpatients).

Comparative characteristics of AF and SR patients are presented in Table 1.

Median CHA_2DS_2-VASc score in the AF group (including 35 patients with valvular AF) was 5 points. Given the diagnosis of HF, all of the AF patients had ≥ 1 point and 211 (98.1%) patients had ≥ 2 points in the CHA_2DS_2-VASc scale.

Primary endpoint

Data on one-year survival were available for all 587 patients. The primary endpoint occurred in 81 of 587 patients (13.8%), including 41 of 215 AF patients (19.1%) and 40 of 372 SR patients (10.8%; p = 0.006), as shown in Table 1. One-year survival probability of both patient groups is presented by the Kaplan-Meier curves in Figure 2. In univariate analysis, AF (compared to SR) was predictive of the primary endpoint in the whole studied population of 587 patients (hazard radio [HR] 1.82; 95% confidence interval [CI] 1.30–2.34, p = 0.01). However, in a multivariate analysis including other variables found to be predictors of the primary endpoint in univariate analyses (i.e. older age, diabetes, higher New York Heart Association [NYHA] class at

Table 1. Baseline characteristics, clinical course of index hospitalisation, and in-hospital and long-term outcomes of patients with atrial fibrillation and in patients in sinus rhythm

	Atrial fibrillation (n = 215)	Sinus rhythm (n = 372)	P
Demographics			
Age [years]	72 (62–79); n = 215	66 (56–76); n = 372	**< 0.0001**
Male	63.7%; 137/215	64.5%; 240/372	0.86
BMI [kg/m^2]	27.8 (24.7–31.6); n = 191	27.5 (24.5–31.5); n = 329	0.65
HF			
LVEF [%]	38 (26.5–48); n = 188	37 (27–50); n = 327	0.92
Previous HF hospitalisation	67.9%; 146/215	50.1%; 186/371	**< 0.0001**
HF aetiology			
Dilated cardiomyopathy	9.3%; 20/215	9.7%; 36/372	1.00
Ischaemic heart disease	51.2%; 110/215	64.3%; 239/372	**0.002**
Hypertensive HF	9.3%; 20/215	12.4%; 46/372	0.28
Valve disease	16.3%; 35/215	8.9%; 33/372	**0.01**
Tachycardia-induced cardiomyopathy	7.0%; 15/215	0.5%; 2/372	**< 0.0001**
Other	7.0%; 15/215	4.6%; 17/372	0.26
Medical history			
Hypertension	69.8%; 150/215	63.4%; 236/372	0.13
Prior PCI or CABG	33%; 71/215	31.5%; 117/371	0.71
Peripheral artery disease	9.8%; 21/215	8.6%; 32/372	0.66
Diabetes	39%; 84/215	31.5%; 117/372	0.07
Chronic kidney disease	29.8%; 64/215	17.5%; 65/371	**<0.0001**
COPD	12.6%; 27/214	12.4%; 46/371	1) 1.00
Stroke	12.2% 26/214	8.4%; 31/371	2) 0.15
Current smoking	49.8%; 102/205	61.8%; 222/359	**0.006**
Previous pharmacotherapy			
Diuretics	71.7%; 147/205	54%; 189/350	**< 0.0001**
Aldosterone antagonist	47.3%; 96/203	37.3%; 130/349	**0.03**
ACE-I	60.6%; 123/203	60.5%; 211/349	1.00
ARB	7.9%; 16/202	8.9%; 31/347	0.75
Beta-blocker	74.9%; 152/203	67.5%; 235/348	0.08
Digoxin	28.9%; 59/204	12.5%; 43/344	**0.0001**
Amiodarone	7.3%; 15/205	4.3%; 15/ 346	0.17
Other antiarrhythmics	4.9%; 10/203	2.6%; 9/346	0.16
Statins	45.8%; 93/203	54.3%; 189/348	0.06
OAC	50.2%; 103/205	10.1%; 35/346	**0.0001**
Antiplatelets	42.7%; 87/204	58.8%; 204/347	**0.0001**
OAC or antiplatelets	79.5%; 163/205	65.6%; 229/349	**0.0005**
Clinical status at admission			
NYHA class	3 (3–4); n = 214	3 (2–3); n = 370	**0.002**
SBP [mm Hg]	130 (110–144); n = 215	130 (120–150); n = 369	0.08
DBP [mm Hg]	80 (70–82); n = 215	80 (70–90); n = 369	**0.004**
Heart rate [bpm]	90 (75–110); n = 215	80 (70–96); n = 370	**< 0.0001**
VF or VT as a cause of admission	4.7%; 10/214	4.6%; 17/ 370	1.00
ACS as a cause of admission	20%; 43/215	38.2%; 141/369	**0.0001**
AF as a cause of admission	41.4%; 89/215	0%; 0/372	**0.0001**

→

Table 1. cont. Baseline characteristics, clinical course of index hospitalisation, and in-hospital and long-term outcomes of patients with atrial fibrillation and in patients in sinus rhythm

	Atrial fibrillation (n = 215)	Sinus rhythm (n = 372)	P
Laboratory findings at admission			
Serum sodium [mmol/L]	138.1 (136–141); n = 212	138.1 (136–141); n = 368	0.84
Serum potassium [mmol/L]	4.4 (4–4.8); n = 211	4.4 (4–4.8); n = 368	0.68
Serum creatinine [mg/dL]	1.15 (0.97–1.43); n = 206	1.04 (0.87–1.3); n = 354	**< 0.0001**
Haemoglobin [g/dL]	13.1 (11.9–14.4); n = 212	13.6 (12.4–14.7); n = 362	**0.02**
Major management during index hospitalisation, clinical status at discharge			
PCI/CABG during hospitalisation	9.3%; 20/215	16.9%; 63/372	**0.01**
AF cardioversion	14.4%; 31/215	NA	NA
Heart rate [bpm]	78 (70–90); n = 210	72 (65–70); n = 357	**< 0.0001**
SBP [mm Hg]	120 (110–130); n = 207	120 (110–130); n = 364	0.36
Pharmacotherapy at hospital discharge			
Diuretics	84.2%; 181/215	80.9%; 300/371	0.37
Aldosterone antagonist	64.2%; 138/215	64.1%; 237/370	1.00
ACE-I	68.8%; 148/215	77.1%; 286/371	**0.03**
ARB	8.4%; 18/215	9.2%; 34/369	0.76
Beta-blocker	85.6%; 184/215	88.1%; 327/371	0.37
Digoxin	42.3%; 91/215	17.8%; 66/371	**0.0001**
Amiodarone	9.3%; 20/215	7.3%; 27/371	0.43
Other antiarrhythmics	5.1%; 11/215	2.2%; 8/371	0.05
Statins	58.1%; 125/215	76.3%; 283/371	**0.0001**
OAC	66.1%; 142/215	22.2%; 82/370	**0.0001**
Antiplatelets	52.6%; 113/215	81.4%; 302/371	**0.0001**
OAC or antiplatelets	91.6%; 197/215	88.4%; 329/372	0.26
In-hospital outcome			
Hospitalisation length [days]	7 (4–11); n = 214	7 (4–10); n = 372	0.20
Death during hospitalisation	5.1%; 11/215	2.4%; 9/372	0.10
One-year outcome			
Death	19.1%; 41/215	10.8%; 40/372	**0.006**
Death or rehospitalisation	48%; 83/173	31.8%; 91/286	**0.0001**

Bolded text indicates p < 0.05. ACE-I — angiotensin-converting-enzyme inhibitor; ACS — acute coronary syndrome; AF — atrial fibrillation; 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; LVEF — left ventricular ejection fraction; NA — not applicable; NYHA — New York Heart Association; OAC — oral anticoagulants; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; VF — ventricular fibrillation; VT — ventricular tachycardia

admission, lower systolic blood pressure at admission, lower serum sodium and haemoglobin concentration at admission, higher heart rate at admission), AF did not prove to be an independent predictive factor of the primary endpoint (HR 0.7; 95% CI 0.41–1.83; p = 0.18).

Univariate analyses of predictors of the primary endpoint, developed separately for AF and SR patients, are shown in Table 2. Variables found to be predictive of the primary endpoint in univariate analyses were consequently included in the multivariate Cox proportional hazards regression models. In multivariate analysis, independent predictors of the primary endpoint in AF patients were: higher NYHA class and higher heart rate at hospital admission, lower serum sodium concentration at admission, and higher heart rate at hospital discharge (Table 3). In SR patients, independent predictors of the primary endpoint included: older age, lower serum sodium concentration at hospital admission, and higher heart rate at discharge (Table 3).

Secondary endpoint

Data on hospital readmissions for decompensated HF were available for 459 patients. The secondary endpoint was

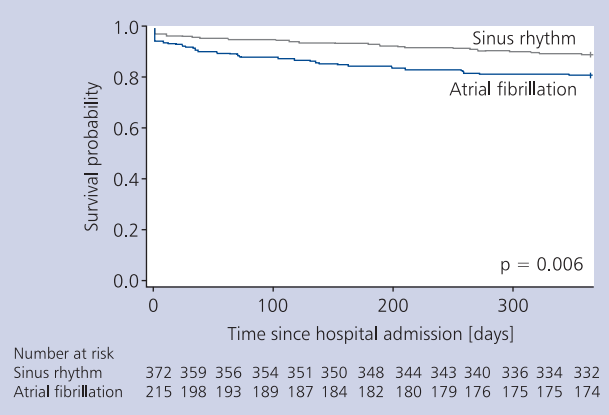

Figure 2. Kaplan-Meier curves for the primary endpoint in patients with atrial fibrillation and in patients with sinus rhythm

reached in 174 of 459 patients (37.9%), including 83 of 173 AF patients (48%) and 91 of 286 SR patients (31.8%; $p < 0.0001$), as shown in Table 1. One-year event-free survival probability of both patient groups is demonstrated by the Kaplan-Meier curves in Figure 3. In univariate analysis, AF (compared to SR) was predictive of the secondary endpoint in the whole group of 459 patients (HR 1.47; 95% CI 1.001–2.16; $p = 0.04$). However, in a multivariate analysis including other variables found to be predictors of the secondary endpoint in univariate analyses (i.e. older age, diabetes, higher NYHA class at admission, prior coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI], lower systolic blood pressure at admission, lower serum sodium and haemoglobin concentration at admission, higher serum creatinine concentration at admission), AF did not prove to be an independent predictive factor of the secondary endpoint (HR 1.07; 95% CI 0.71–1.62; $p = 0.74$).

In AF patients, diabetes (HR 1.95; 95% CI 1.25–3.04; $p = 0.003$), prior coronary revascularisation (PCI or CABG) (HR 1.557; 95% CI 0.94–2.31; $p = 0.09$), and lower serum sodium concentration at admission (HR 0.93; 95% CI 0.89–0.97; $p = 0.001$) were predictive of the secondary endpoint in univariate analyses. In a multivariate analysis, only diabetes (HR 1.95; 95% CI 1.25–3.04; $p = 0.003$) and lower admission sodium concentration (HR 0.93; 95% CI 0.89–0.97; $p = 0.001$) remained predictors of the secondary endpoint in AF patients.

In SR patients, a history of previous HF hospitalisation (HR 1.55; 95% CI 1.02–2.36; $p = 0.04$), lower left ventricular ejection fraction (LVEF) (HR 0.98; 95% CI 0.96–0.996; $p = 0.01$), higher NYHA class at hospital admission (HR 1.58; CI 1.19–2.10; $p = 0.001$), lower systolic blood pressure at admission (HR 0.99; CI 0.98–0.997; $p = 0.007$), lower admission serum sodium (HR 0.94; CI 0.89–0.99; $p = 0.02$) and haemoglobin concentrations (HR 0.88; CI 0.79–0.98; $p = 0.02$), and higher creatinine concentration at admission (HR 1.29; CI 1.03–1.62; $p = 0.03$) were predictive of the secondary endpoint in univariate analyses, and they were consequently included in the multivariate Cox proportional hazards regression model. None of those variables remained an independent prognostic factor in multivariate analysis.

DISCUSSION

AF is the most common arrhythmia in HF. The prevalence of AF in HF patients in large clinical trials varies between 20% and 48% [2, 13–15], depending on the severity of HF. In our analysis, AF was present in 37% of HF patients, which is similar to the prevalence of 38% reported in a previous large Polish HF registry conducted within the Polish National Cardiovascular Disease Prevention and Treatment Program, POLKARD 2003–2005 [15].

Frequent HF and AF coexistence results from multiple pathophysiological mechanisms. HF may arise as a consequence of tachycardiomyopathy or decompensation in acute-onset AF [1, 5]. On the other hand, HF predisposes to arrhythmia due to increased atrial pressure, chronic neurohormonal stimulation, electrophysiological disturbances secondary to cardiac remodelling and fibrosis, valvular dysfunction, and volume overload [1, 5]. It is postulated that valvular heart disease is the strongest factor predisposing to AF development, whereas coronary artery disease (CAD) favours SR-HF [15–18]. In our study, valvular heart disease and tachycardia-induced cardiomyopathy were more prevalent in the AF group, and CAD — in the SR group.

Based on previously published studies, AF–HF patients are more likely than SR–HF subjects to have cardiovascular risk factors and pre-existing disease at baseline, including older age, hypertension, valvular disease, diabetes, renal failure, stroke, and chronic obstructive pulmonary disease [15, 17, 18]. Similarly, in our analysis, we observed significant differences in baseline parameters between the two subgroups. HF patients with AF were older, more often had a history of previous HF hospitalisation, had lower haemoglobin concentration, and more frequently had a history of chronic kidney disease with higher serum creatinine concentration at hospital admission. There was also a higher incidence of previous stroke in the AF–HF group, but the difference was not statistically significant, which was probably attributable to more frequent anticoagulant treatment in AF patients.

The presence of AF at hospital admission is associated with more pronounced HF symptomatology. In HF, the prevalence of AF increases from 10% in NYHA class I patients to 50% in NYHA class IV patients [5, 15, 18]. In our study, AF patients were characterised by a worse clinical status at hospital admission, including not only higher heart rate, but also higher NYHA class and lower diastolic blood pressure. Consequently, AF patients more often required aldosterone antagonists and loop diuretics before index hospitalisation. Interestingly, LVEF did not differ between AF and SR patients.

Table 2. Univariate analyses of predictors of death at one year in both groups

	Atrial fibrillation		Sinus rhythm	
	HR (95% CI)	P	HR (95% CI)	P
Demographics				
Age [per 10 years]	1.02 (0.995–1.06)	0.11	**1.05 (1.02–1.07)**	**0.001**
Male	0.78 (0.42–1.45)	0.44	0.83 (0.44–1.56)	0.56
BMI [per 1 kg/m^2]	0.93 (0.87–1.001)	0.06	0.98 (0.91–1.05)	0.54
Heart failure				
LVEF [per 5%]	**0.97 (0.95–0.998)**	**0.03**	0.99 (0.97–1.02)	0.57
Previous HF hospitalisation	0.80 (0.43–1.52)	0.50	0.98 (0.53–1.83)	0.96
Medical history				
Hypertension	1.41 (0.69–2.88)	0.34	1.07 (0.56–2.05)	0.84
Coronary artery disease	1.52 (0.81–2.89)	0.19	1.92 (0.94–3.92)	0.08
Prior PCI or CABG	1.64 (0.89–3.04)	0.12	0.92 (0.47–1.82)	0.82
Peripheral artery disease	1.37 (0.54–3.50)	0.51	1.18 (0.42–3.32)	0.75
Diabetes	1.79 (0.97–3.30)	0.06	1.50 (0.80–2.83)	0.21
COPD	0.54 (0.17–1.75)	0.31	1.25 (0.53–2.99)	0.61
Stroke	0.57 (0.18–1.84)	0.34	0.89 (0.27–2.87)	0.84
Current smoking	0.91 (0.48–1.72)	0.77	0.99 (0.52–1.88)	0.97
Clinical status at admission				
NYHA class	**1.99 (1.20–3.29)**	**0.01**	**1.77 (1.15–2.73)**	**0.01**
SBP [per 10 mm Hg]	**0.98 (0.97–0.997)**	**0.02**	0.99 (0.98–1.005)	0.29
Heart rate [per 10 bpm]	**1.01 (1.00–1.02)**	**0.047**	1.01 (0.998–1.03)	0.09
VF or VT as a cause of admission	1.08 (0.26–4.46)	0.92	1.05 (0.25–4.34)	0.95
ACS as a cause of admission	1.74 (0.89–3.41)	0.11	1.50 (0.81–2.79)	0.20
Laboratory findings at admission				
Serum sodium [per 1 mmol/L]	**0.91 (0.87–0.95)**	**< 0.0001**	**0.87 (0.82–0.93)**	**< 0.0001**
Serum creatinine [per 1 mg/dL]	0.995 (0.93–1.07)	0.89	1.33 (0.97–1.82)	0.08
Haemoglobin [per 1 g/dL]	0.94 (0.81–1.09)	0.42	**0.82 (0.71–0.94)**	**0.006**
Major management during index hospitalisation, clinical status at discharge				
PCI/CABG during hospitalisation	1.33 (0.52–3.39)	0.55	1.06 (0.47–2.39)	0.90
AF cardioversion	1.26 (0.56–2.84)	0.58	NA	NA
Heart rate [per 10 bpm]	**1.02 (1.004–1.03)**	**0.01**	**1.03 (1.008–1.05)**	**0.006**

Bolded text indicates p < 0.05. HR — hazard ratio; CI — confidence interval; ACS — acute coronary syndrome; AF – atrial fibrillation; BMI — body mass index; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; HF — heart failure; LVEF — left ventricular ejection fraction; NA— not applicable; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; VF — ventricular fibrillation; VT — ventricular tachycardia

Our study also showed significant differences in discharge pharmacotherapy between AF–HF and SR–HF patients. Beta-blockers were equally often prescribed to patients in SR and to patients with AF, while digoxin was, understandably, more often given to AF patients (as more than a half of the AF group had permanent AF). Adequate control of ventricular rate in AF may reduce HF symptoms by improving haemodynamics and prevent the development of tachycardiomyopathy. However, a recently published meta-analysis indicates that HF patients with concomitant AF and HF patients with SR differ in response to beta-blocker therapy and that beta-blockers, routinely used as first-line drugs in HF, do not improve prognosis in HF–AF patients [11]. According to Kotecha et al. [11], this finding could be partly explained by structural and cellular changes in the course of AF, which might affect the efficacy of the beta-blocker therapy. Furthermore, in AF patients, irregular rhythm itself has also a detrimental effect on systolic and diastolic heart function, irrespective of heart rate [11]. Nevertheless, a combination of a beta-blocker and digitalis may be beneficial in HF patients with permanent AF [1, 19]. However, the relatively high incidence of therapy with digoxin (a drug with class IIb indication in HF according to the

Table 3. Multivariate analyses of predictors of death at one year in both groups

	Atrial fibrillation		Sinus rhythm	
	HR (95% CI)	P	HR (95% CI)	P
Age [per 10 years]	NA		**1.04 (1.01–1.07)**	**0.007**
LVEF [per 5%]	0.97 (0.95–1.004)	0.09	NA	
NYHA class at admission	**1.95 (1.11–3.42)**	**0.02**	1.40 (0.88–2.26)	0.16
SBP at admission [per 10 mm Hg]	1.00 (0.99-1.02)	0.83	NA	
Serum sodium at admission [per 1 mmol/L]	**0.89 (0.85–0.94)**	**0.0001**	**0.87 (0.79–0.94)**	**0.0006**
Haemoglobin at admission [per 1 mg/dL]	NA		0.90 (0.76–1.07)	0.22
Heart rate at admission [per 10 bpm]	**1.02 (1.001–1.03)**	**0.04**	NA	
Heart rate at discharge [per 10 bpm]	**1.02 (1.01–1.04)**	**0.01**	**1.03 (1.01–1.05)**	**0.008**

Bolded text indicates p <0.05. HR — hazard ratio; CI — confidence interval; LVEF — left ventricular ejection fraction; NA — not applicable (variable not included in the multivariate analysis); NYHA — New York Heart Association; SBP — systolic blood pressure

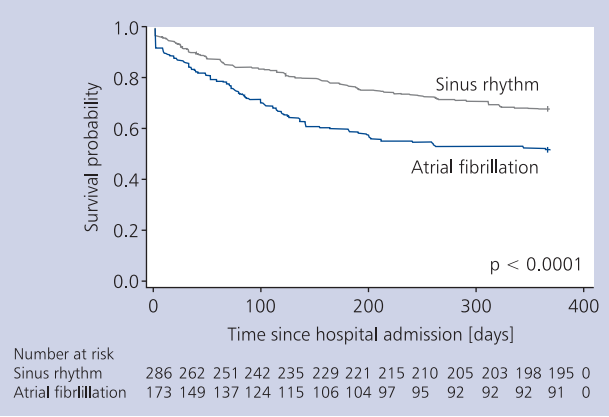

Figure 3. Kaplan-Meier curves for the secondary endpoint in patients with atrial fibrillation and in patients with sinus rhythm

current ESC guidelines [19]) in SR patients (17.8%) observed in our study might seem surprising, given the suboptimal frequency of treatment with first-line HF medications, such as beta-blockers (88.1%), angiotensin-converting enzyme inhibitors (ACE-I) (77.1%), and aldosterone antagonists (64.1%).

Despite the same degree of left ventricular dysfunction, comparable systolic blood pressure and more pronounced HF symptoms, AF patients were less frequently prescribed ACE-I at discharge compared to SR patients. This may be partly explained by worse renal function in AF patients; however, the observed creatinine concentrations with a median of 1.15 mg/dL hardly translate into glomerular filtration rate values that would justify waiving ACE-I treatment. The SR group was also significantly more often prescribed statins, which may be partly due to the higher incidence of CAD in these patients. Unfortunately, no data on cholesterol concentrations were available in the ESC-HF Pilot. It should be noted that some evidence indicates that treatment with ACE-I and statins might be beneficial in AF patients because of their antiarrhythmic properties, and may be considered for the prevention of new-onset AF in patients with HF [1]. However, more than half of the AF patients in our study had permanent AF.

As expected, due to higher prevalence of CAD, SR patients were more frequently prescribed antiplatelet agents, while AF patients more often received oral anticoagulants (OAC). Nevertheless, the frequency of OAC therapy in the AF–HF group was relatively low, given that 98.1% of AF patients had at least two points in the CHA_2DS_2-VASc scale and, consequently, a class I indication for OAC treatment, with the remaining 1.9% of AF patients with one point and, thus, a class IIa indication for OAC therapy [1]. To simplify presentation of the results, CHA_2DS_2-VASc score was calculated for the whole AF group, including patients with underlying valve disease, even though patients with valvular AF have indications for OAC therapy independently of the CHA_2DS_2-VASc score. Half of AF patients did not receive OAC before index admission and as many as one third were not prescribed OAC at hospital discharge. Many of those patients received antiplatelet therapy instead. However, according to the current recommendations, antiplatelet therapy should not replace OAC and is reserved only for those patients who refuse to take any form of OAC (including non-vitamin K antagonist OAC) [1]. In previous surveys, the frequency of OAC use in AF–HF patients was even lower, ranging from 32% to 55% [15, 17].

Compared to SR–HF patients, AF–HF patients are characterised by higher short- and long-term mortality after hospital discharge [9, 14, 20]. There is also evidence that HF patients with AF are at increased risk of hospital readmissions [6–9, 14, 20]. The association of AF with these unfavourable outcomes is similar in patients with HF with preserved LVEF and in patients with HF with reduced LVEF [8]. However, so far, it is unclear whether AF itself is an independent risk factor of death and rehospitalisation in HF or whether it is merely a marker of older age, higher disease burden, and more advanced HF. In our study, in one-year follow-up, AF patients were at higher

risk of all-cause death as well as death or rehospitalisation than SR patients, but AF did not prove to be an independent predictor of the primary or the secondary endpoint. These findings are largely consistent with the previous trials [13–16, 18]. Most of the studies suggest that AF acts as a marker of neurohormonal activation reflecting HF severity [1, 5]. On the other hand, there are some reports showing that patients with AF at baseline have higher all-cause mortality and higher rate of readmissions than patients with SR, independently of other risk factors [20, 21].

The results of our analysis indicate that AF–HF patients differ from SR–HF patients not only with regard to baseline characteristics and long-term outcome, but also in terms of prognostic factors. In previous studies, both admission and discharge heart rate were proven to be associated with long-term mortality of hospitalised HF patients [22, 23]. In our analysis, heart rate at hospital discharge was an independent predictor of one-year survival in both subgroups. Additionally, heart rate at hospital admission was an independent prognostic factor in patients with AF, but not in SR patients. Likewise, higher NYHA class at hospital admission was predictive of the primary endpoint in AF patients, but not in the SR group. These differences in prognostic factors between the two subgroups might be partly attributable to the (although not significantly) higher in-hospital mortality observed in AF patients: as in-hospital deaths accounted for approximately one quarter of primary outcome events, risk factors for in-hospital death (including worse clinical status at hospital admission, i.e. higher heart rate and higher NYHA class at admission) might have gained significance in the analysis of predictors of the primary endpoint [22]. Furthermore, recent studies have reported differences in the impact of heart rate on prognosis between AF–HF and SR–HF patients [23, 24].

In our previous studies, conducted in Polish ESC-HF Pilot participants, hyponatraemia at hospital admission was associated with death during hospitalisation, death at one year, as well as death or hospital readmission at one year [22, 25]. In the current analysis, lower admission sodium concentration proved to be predictive of death at one year in both studied subgroups, as well as of death or rehospitalisation for HF at one year in AF patients. In HF, hyponatraemia largely results from the augmented secretion of arginine vasopressin and is often exacerbated by loop diuretics [26]. In AF patients, hyponatraemia may be also triggered by the use of antiarrhythmic drugs [26].

Limitations of the study

In contrast to randomised clinical trials, the advantage of registries is that they include "real-world" patients. However, they are also related to serious limitations, such as their observational character and incompleteness of data. We had only access to the data that were available in the registry and collected in the way pre-established by its coordinators. ESC-HF Pilot case report forms enabled investigators to choose only one (leading) heart rhythm, without an opportunity to determine whether patients with paced rhythm had underlying AF or not. Therefore, there may be some minor inaccuracy in the prevalence of AF in patients hospitalised for HF in our study, although it is similar to the AF prevalence observed in the POLKARD registry [15].

Furthermore, we did not have data on the number of AF patients referred for percutaneous ablation before index hospitalisation, although it might be assumed that in the studied group of patients with HF (and thus with atrial enlargement and remodelling) it was not a significant proportion. During index hospitalisation, only two of 215 patients underwent AF ablation, so this parameter was not included in the analysis.

In the present study, data on hospital readmissions at one year were missing for 128 patients, leaving 459 patients (78.2% of 587 patients) for the secondary endpoint analysis. Given the relatively small size of the study groups, it was necessary to limit the number of variables included in the Cox proportional hazards regression analysis in order to achieve adequate events per predictor variable value. Probably due to the small size of the group, no factor has obtained statistical significance in the multivariate analysis of the secondary endpoint in SR patients.

CONCLUSIONS

Patients with AF are a peculiar subpopulation of HF patients, and they differ significantly from HF patients in SR. The results of our study suggest that Polish HF patients with concomitant AF do not receive optimal pharmacological treatment, especially in terms of anticoagulant therapy. In the studied group of hospitalised HF patients, serum sodium concentration at hospital admission and heart rate at hospital discharge were independent prognostic factors in patients with AF and patients in SR. In contrast to SR patients, heart rate in AF patients at hospital admission was also predictive of long-term mortality.

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Charakterystyka kliniczna i czynniki prognostyczne w rocznej obserwacji pacjentów z niewydolnością serca i migotaniem przedsionków w porównaniu z chorymi z niewydolnością serca i rytmem zatokowym

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Streszczenie

Wstęp: Migotanie przedsionków (AF) często współistnieje z niewydolnością serca (HF).

Cel: Celem pracy była ocena charakterystyki klinicznej i identyfikacja czynników prognostycznych w rocznej obserwacji pacjentów hospitalizowanych z powodu HF w zależności od tego, czy był u nich obecny rytm zatokowy (SR) czy występowało u nich AF.

Metody: Badaniem objęto pacjentów uczestniczących w polskiej części Pilotażowego Rejestru Niewydolności Serca Europejskiego Towarzystwa Kardiologicznego, hospitalizowanych z powodu HF i poddanych rocznej obserwacji po wypisaniu ze szpitala. Pacjenci z wszczepionym układem stymulującym zostali wyłączeni z badania. Pierwotny punkt końcowy stanowił zgon z jakiejkolwiek przyczyny po roku obserwacji. Wtórny, złożony punkt końcowy obejmował zgon z jakiejkolwiek przyczyny i powtórną hospitalizację z powodu zaostrzenia objawów HF po roku obserwacji.

Wyniki: Do ostatecznej analizy włączono 587 pacjentów. Migotanie przedsionków stwierdzono u 215 (36,6%) osób. W porównaniu z chorymi z SR, pacjenci z AF byli starsi, w przeszłości byli częściej hospitalizowani z powodu HF, a przy przyjęciu do szpitala charakteryzowali się wyższą klasą czynnościową wg *New York Heart Association* (NYHA), wyższą częstością rytmu serca, niższym rozkurczowym ciśnieniem tętniczym, wyższym stężeniem kreatyniny i niższym stężeniem hemoglobiny. Śmiertelność wewnątrzszpitalna była wyższa w grupie pacjentów z AF niż u chorych z SR (5,1% *vs*. 2,4%), ale różnica ta nie osiągnęła istotności statystycznej ($p = 0,1$). Pierwotny punkt końcowy wystąpił u 21 z 215 pacjentów z AF (19,1%) oraz u 40 z 372 osób z SR (10,8%; $p = 0,006$). W analizie wieloczynnikowej predyktorami pierwotnego punktu końcowego w grupie z AF były: wyższa klasa NYHA przy przyjęciu do szpitala ($p = 0,02$), wyższa częstość rytmu serca przy przyjęciu ($p = 0,04$), niższe stężenie sodu przy przyjęciu ($p = 0,0001$) i wyższa częstość rytmu serca przy wypisaniu ze szpitala ($p = 0,01$). W grupie pacjentów z SR niezależnymi czynnikami predykcyjnymi wystąpienia pierwotnego punktu końcowego były: starszy wiek ($p = 0,007$), niższe stężenie sodu przy przyjęciu ($p = 0,0006$) i wyższa częstość rytmu serca przy wypisaniu ze szpitala ($p = 0,008$). Dane dotyczące powtórnej hospitalizacji z powodu HF były dostępne w przypadku 459 pacjentów. Wtórny punkt końcowy wystąpił u 83 ze 173 chorych z AF (48%) oraz u 91 z 286 pacjentów z SR (31,8%; $p < 0,0001$). W grupie osób z AF niezależnymi czynnikami predykcyjnymi wystąpienia wtórnego punktu końcowego były cukrzyca ($p = 0,003$) i niższe stężenie sodu przy przyjęciu ($p = 0,001$).

Wnioski: Pacjenci z HF i towarzyszącym AF znacząco różnią się od chorych z HF i SR. W badanej populacji osób z HF stężenie sodu przy przyjęciu i częstość rytmu serca przy wypisaniu ze szpitala były niezależnymi czynnikami prognostycznymi zarówno w grupie z AF, jak i SR. W przeciwieństwie do pacjentów z SR, u chorych z AF również częstość rytmu serca przy przyjęciu do szpitala okazała się predyktorem wystąpienia zgonu w obserwacji długoterminowej.

Słowa kluczowe: migotanie przedsionków, rytm zatokowy, niewydolność serca, hospitalizacja, rokowanie

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