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ORIGINAL ARTICLE

Heart failure in patients with atrial fibrillation: Insights from Polish part of the EORP-AF general long-term registry

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Abstract

Aims This study aimed to determine the impact of heart failure (HF) on clinical outcomes in patients with atrial fibrillation (AF).

Methods and results We analysed data from Polish participants of the EURObservational Research Programme-AF General Long-Term Registry. The primary endpoint was all-cause death, and the secondary endpoints included hospital readmissions, cardiovascular (CV) interventions, thromboembolic and haemorrhagic events, rhythm control interventions, and other CV or non-CV diseases development during one-year follow up. Overall, 688 patients with available data on HF were included into analysis; 51% (n = 351) had HF; of these 48% (n = 168) had reduced ejection fraction (HFrEF), 22% (n = 77) mid-range EF (HFmrEF), and 30% (n = 106) preserved EF (HFpEF). Compared with patients without HF, those with HF had higher mortality rate (aHR 5.61; 95% CI 1.94–16.22, $P < 0.01$). Patients with HF (vs. without HF) had more often CV interventions (10% vs. 5.4%, $P = 0.046$) and events (14% vs. 7.1%, $P = 0.02$), and had less often atrial arrhythmia-related hospital admissions (6.8% vs. 15%, $P < 0.01$). Over follow-up, patients with HFmrEF and HFpEF had similar mortality rate versus HFrEF (aHR 0.45, 95% CI 0.13–1.57, $P = 0.45$ for HFmrEF and aHR 0.54, 95% CI 0.20–1.48, $P = 0.54$ for HFpEF). Mortality rate was similar among rhythm versus rate control group (aHR 0.34; 95% CI 0.10–1.16; $P = 0.34$).

Conclusions AF patients with HF have greater mortality rate and more CV interventions/events. No statistically significant difference in long-term outcomes between patients with HFrEF, HFmrEF, and HFpEF highlights the need to develop therapeutic strategies targeting functional status and survival for patients with HF and AF.

Keywords Atrial fibrillation; Heart failure; Preserved ejection fraction; Reduced ejection fraction; Mid-range ejection fraction

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Introduction

Heart failure (HF) and atrial fibrillation (AF) are conditions that can cause and exacerbate each other through similar pathophysiological mechanisms and risk factors.[1] HF can co-exist in more than 50% of patients with AF[2] and the incidence of first HF symptoms within 12 months of diagnosing AF is 7.8%, up to 24% over the next 5 years.[3] Despite advances in treatment, hospitalized patients with AF and HF remain at high mortality and re-hospitalization rates.[4,5]

There are significant differences in terms of pathophysiology, clinical features and the effectiveness of HF treatment

depending on its phenotype, that is, HF with reduced ejection fraction (HFrEF), mid-range EF (HFmrEF) or preserved EF (HFpEF). In addition, the diagnosis of HFpEF or HFmrEF in patients with AF is more difficult because the elevation of natriuretic peptide levels and enlargement of the left atrium (LA) (which are diagnostic criteria for HFmrEF and HFpEF) may be associated with arrhythmia instead of HF per se.[1] The aim of the study was to present the clinical characteristics, treatment used and long-term outcomes of AF patients with concomitant HF taking into account the HF subgroups (HFrEF, HFmrEF, and HFpEF).

Methods

Study design and enrolled patients

The EURObservational Research Program on Atrial Fibrillation General (EORP-AF) Long Term General Registry is a prospective, international, observational survey, with 250 cardiology centres from 27 European countries participating. The registry included consecutive patients aged ≥18 years presenting to cardiologists with AF as the main or comorbid condition. The registry was approved by local ethical review boards according to the regulations of each participating country. A signed, informed consent was obtained from each patient after providing detailed information on the registry.[6] Data on clinical characteristics, diagnostic tests performed, and implemented treatment collected at baseline, and at visit after 1 year were taken into account in this analysis. We performed three group of patients' analyses. First analysis regarded comparison of patients with and without HF, second analysis presented HF subgroups comparison (HFrEF, HFmrEF, and HFpEF) and third analysis compared rhythm and rate control treatment among HF patients.

Heart failure subgroups

Patients with an EF of <40%, 40%–49% and ≥50% were included in the HFrEF, HFmrEF, and HFpEF groups, respectively. To verify the pertinence of HF diagnosis in patients with EF ≥ 40%, we assessed whether they met the echocardiographic criteria for HFpEF and HFmrEF according to the European Society of Cardiology (ESC) HF guidelines,[7] that is, the presence of left ventricular hypertrophy (LVH) and/or LA enlargement (defined as indexed LA volume index >34 mL/m^2) and/or LV diastolic dysfunction [information was given dichotomically (yes vs. no) in case report form (CRF)]. Due to missing data on LA volume index, the LA dimension of >40 mm was used as criterion of LA enlargement. We also evaluated plasma concentrations of B-type natriuretic peptide (BNP) and/or of N-terminal pro-BNP (NT-proBNP), and adopted a threshold of ≥35 pg/mL for BNP levels and of ≥125 pg/mL for NT-proBNP as justifying HF suspicion in patients in the non-acute setting and BNP ≥ 100 pg/mL and NT-proBNP ≥300 pg/mL in patients hospitalized for exacerbation of HF. We applied ESC HF guidelines from 2016, as the registry was conducted in the European population and the study was conducted between 2013 and 2016.

Rate and rhythm control strategy

For the rate control strategy of AF treatment, beta-blockers, digoxin, diltiazem, or verapamil were used to control the heart rate. For the rhythm control strategy of AF treatment, dronedarone, flecainide, propafenone, sotalol, and amiodarone were used to maintain the sinus rhythm and the choice of particular drug depended on the presence or absence of a structural heart disease. For active rhythm control, electrical cardioversion and catheter ablation were performed in selected patients. The type of treatment was dependent on the decision of the treating physician.

Clinical outcomes

The primary endpoint was all-cause death at 1 year. The secondary endpoints included hospital readmissions, cardiovascular interventions, thromboembolic (TE) and haemorrhagic events (HE), rhythm control interventions, and other cardiovascular or non-cardiovascular diseases development at 1 year. We assessed the frequency of the primary and the secondary endpoints in following groups: patients with and without HF; subgroups of HF patients; HF patients on rhythm and rate control strategy treatment.

Statistical analysis

All statistical analyses were conducted using the SAS software, version 9.2 (SAS Institute Inc., Cary, NC). Normal distribution was assessed through the Shapiro–Wilk test; variables with normal distribution were presented as mean ± SD, and variables with non-normal distribution were presented as median and interquartile range (IQR). The groups were compared using the Fisher's exact test (two groups comparison) and Chi-square test (three or more groups comparison) for categorical variables and the t-test (two groups comparison) and one-way ANOVA (three or more groups comparison). Cox proportional hazards models (HR) with 95% coincidence interval (CI) were used to estimate the hazard of (1) HF versus no HF; (2) HFpEF and HFmrEF compared with HFrEF; and (3) rhythm control compared with rate control strategy for time to all-cause death without and with adjustment for sex, age and other CHA_2DS_2-VAS_C score components: hypertension, vascular disease, diabetes, previous thromboembolic events. All tests

were two-tailed. For all tests, a P value of <0.05 was deemed significant.

Results

The current analysis included the 701 consecutive Polish patients hospitalized for AF, enrolled in years 2013–2016. Of 701 patients enrolled, 13 were excluded due to missing data on HF occurrence. In the overall cohort, 51% of patients had HF, of whom 15% had dilated cardiomyopathy, and 3.4% hypertrophic cardiomyopathy diagnosed. Baseline characteristic and comparison of both groups were presented in *Table 1*.

As compared with HFrEF and HFmrEF patients, those with HFpEF were older, more often were female, had more often asymptomatic AF (EHRA I), and less often had long-standing persistent AF, coronary artery disease. HFpEF had higher thromboembolic risk based on CHA_2DS_2-VASc score. Patients with HFrEF had less prevalent sinus rhythm on electrocardiogram, and more often had liver disease. There were no statistically significant differences between analysed HF subgroups in relation to antithrombotic treatment, rate and rhythm control strategies (see *Table 2*).

Among AF patients with HF those in rate control group was characterized by more severe HF symptoms (NYHA III/IV class), valvular diseases, device therapy, previous occurrence of TE, HE, as well as enlarged left ventricular diastolic diameter. Diuretic and mineralocorticoid receptor antagonists were more often prescribed among rate control group (see *Table 3*).

Long-term outcomes

Compared with patients without HF, those with HF had higher mortality rate (aHR 5.61; 95% CI 1.94–16.22, $P < 0.01$) (*Figure 1*; panel A). When compared with those without HF, those with HF during follow-up period had more often cardiovascular (CV) interventions (10% vs. 5.4%, $P = 0.046$), more often hospital readmissions due to CV events (14% vs. 7.1%, $P = 0.02$), mainly because of worsening of HF and chronic kidney disease development (9.0% vs. 2.1%, $P < 0.01$) and less often electrical cardioversion (4.6% vs. 10%, $P = 0.02$) (see *Table 4*). In sub-analysis of patients with HF, there were no statistically significant difference in long-term outcomes between patients with first detected AF versus those with persistent/permanent AF (*Table S1*).

There was no statistically significant difference in CV interventions, hospital readmissions due to CV events, TE and HE in long-term observation among subgroups of HF patients (see *Table 5*) as well as among HF patients on rate or rhythm control strategy (see *Table 6*).

Over follow-up, patients with HFmrEF and HFpEF had similar mortality rate to those with HFrEF (aHR 0.45, 95% CI 0.13–1.57, $P = 0.45$ for HFmrEF and aHR 0.54, 95% CI 0.20–1.48, $P = 0.54$ for HFpEF) (*Figure 1*; panel B). Mortality rate was similar among rhythm control group versus rate control group (aHR 0.34; 95% CI 0.10–1.16; $P = 0.34$) (*Figure 1*; panel C).

Discussion

The major findings of this study are as follows: (i) AF patients with HF have higher mortality rate as compared with those without HF; and (ii) there were no statistically significant difference in long-term outcomes among patients with HFrEF, HFmrEF, and HFpEF, although some numerical trends were evident for worse mortality rate in HFrEF.

Although similar TE rate during the one-year follow-up period, AF patients with HF had a higher mortality rate as compared with those without HF. Our data are in line with Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) study. Compared with patients without HF, those with HF had similar stroke rate but higher mortality and hospitalization rates.[8] The authors of the cited work concluded that patients with HF were older, suffered from hypertension more often and had a significantly higher unadjusted stroke risk compared with those without HF.[8] However, this association was no longer significant after adjustment for the aforementioned risk factors, what may suggest that hypertension and age are more significant predictors of stroke risk compared with HF.[8] The other reason of this finding could be low stroke rate in their cohort.[8] Moreover, number of patients might be not large enough to detect a difference between groups.[8]

A recent meta-analysis of clinical trials comparing non-vitamin K (VKA) oral anticoagulants (NOACs) to VKA in patients with AF found that rates of stroke and systemic embolism were comparable in AF patients with and without HF, but patients with HF had increased all-cause and cardiovascular mortality rates.[9] In the Polish part of the HF Pilot Register of the European Society of Cardiology, almost 50% of patients with HF and concurrent AF experienced re-hospitalization or died in the first year of follow-up.[10] These results suggest that outpatient care in Poland may be suboptimal and illustrate the important role of registers that analyse the data of 'real-life' patients and enable the assessment of risk factors and an appropriate management plan.

The difference in mortality rate between patients with HFrEF, HFmrEF, and HFpEF was not statistically significant, however, the trend in favour of a higher mortality rate in patients with HFrEF was observable ($P < 0.15$). The low number of events of death may be the reason why statistical significance was not achieved in the case of this comparison. Previous studies have shown inconsistent results on survival in AF patients with various HF populations, with similar,[11–14]

Table 1 Characteristics of patients with atrial fibrillation with/without concomitant heart failure

Variable	HF (n = 351)	Without HF (n = 337)	P
Demographics			
Age, years	69 ± 11	65 ± 12	<**0.01**
Female, n (%)	138 (39%)	154 (46%)	0.11
BMI, kg/m^2	29 ± 4.8; *n = 334*	29 ± 4.5; *n = 313*	0.37
AF, n (%)			
AF first detected	18 (5.1%)	23 (6.8%); *n = 336*	0.42
AF paroxysmal	76 (22%)	139 (41%); *n = 336*	<**0.01**
AF long-standing persistent	34 (9.7%)	27 (8.0%); *n = 336*	0.50
AF persistent	59 (17%)	81 (24%); *n = 336*	**0.02**
AF permanent	164 (47%)	23 (6.8%); *n = 336*	<**0.01**
EHRA I	180 (51%)	120 (36%)	<**0.01**
EHRA II	86 (25%)	140 (42%)	<**0.01**
EHRA III-IV	85 (24%)	76 (22%)	1.00
Concomitant diseases, n (%)			
Hypertension	202 (58%); *n = 349*	197 (58%); *n = 337*	0.94
Coronary artery disease	158 (48%); *n = 330*	87 (26%); *n = 330*	<**0.01**
NYHA III/IV	132 (38%)	NA	**NA**
Valvular disease	170 (50%); *n = 343*	63 (19%); *n = 336*	<**0.01**
Device therapy (PM/CRT/ICD)	90 (26%)	36 (11%)	<**0.01**
Dilated cardiomyopathy	54 (15%)	1 (0.3%)	<**0.01**
Hypertrophic cardiomyopathy	12 (3.4%)	3 (0.9%)	**0.03**
COPD	35 (10%); *n = 350*	12 (3.6%); *n = 336*	<**0.01**
CKD	78 (22%)	30 (8.9%)	<**0.01**
Diabetes mellitus	129 (37%); *n = 350*	63 (19%); *n = 332*	<**0.01**
Liver disease	12 (3.4%); *n = 350*	0 (0%); *n = 336*	<**0.01**
Smoking (current/former)	116 (35%); *n = 336*	98 (30%); *n = 329*	0.21
Thromboembolic and bleeding risk, n (%)			
Previous TE	52 (15%); *n = 349*	27 (8.0%)	<**0.01**
Malignancy (current/former)	17 (4.9%); *n = 348*	20 (6.0%); *n = 335*	0.61
CHA_2DS_2-VASc score	4.0 ± 1.7	2.3 ± 1.6	<**0.01**
Previous HE	38 (11%); *n = 350*	18 (5.4%); *n = 336*	**0.01**
Anaemia	33 (9.4%)	11 (3.3%)	<**0.01**
Bleeding predisposition	31 (8.9%); *n = 350*	5 (1.5%); *n = 336*	<**0.01**
HAS-BLED score	1.2 ± 1.1	1.8 ± 1.6	<**0.01**
Electrocardiogram parameters			
Sinus rhythm	69 (20%)	128 (38%)	<**0.01**
AF/atrial flutter rhythm	246 (70%)	194 (58%)	<**0.01**
PM rhythm	36 (10%)	14 (4.2%)	<**0.01**
Heart rate, b.p.m.	81 ± 19; *n = 350*	81 ± 22	0.75
PR interval, ms	173 ± 44; *n = 66*	169 ± 33; *n = 113*	0.54
QRS complex, ms	108 ± 26; *n = 294*	96 ± 15; *n = 265*	<**0.01**
Bundle branch block, n (%)	65 (20%); *n = 333*	23 (7.5%); *n = 308*	<**0.01**
Echocardiography parameters			
LA, mm	49 ± 8.6; *n = 309*	44 ± 6.7; *n = 261*	<**0.01**
LVDD, mm	55 ± 13; *n = 308*	54 ± 9.4; *n = 263*	<**0.01**
LVEF, %	42 ± 9.7; *n = 301*	50 ± 6.0; *n = 255*	<**0.01**
LVH, n (%)	77 (25%); *n = 308*	49 (19%); *n = 263*	0.11
Laboratory parameters			
Haemoglobin, mg/dL	13 ± 1.8; *n = 333*	14 ± 1.4; *n = 316*	<**0.01**
Creatinine, mg/dL	1.2 ± 0.5; *n = 331*	1.0 ± 0.4; *n = 312*	<**0.01**
NT-proBNP, pg/mL	3583 ± 4089; *n = 84*	1308 ± 1325; *n = 40*	<**0.01**
Treatment [n (%)]			
VKA	201 (57%); *n = 350*	163 (48%)	**0.02**
NOAC	107 (31%); *n = 350*	140 (42%)	<**0.01**
ACE inhibitors/ARBs	275 (80%); *n = 347*	224 (67%); *n = 336*	<**0.01**
Diuretics	260 (75%); *n = 347*	129 (38%); *n = 336*	<**0.01**
MRA	178 (51%); *n = 347*	48 (14%); *n = 336*	<**0.01**
Beta-blockers	300 (86%); *n = 347*	249 (74%); *n = 335*	<**0.01**
Non-dihydropyridine-CCB	11 (3.2%); *n = 347*	2 (0.6%); *n = 335*	**0.02**
Dihydropyridine-CCB	47 (14%); *n = 347*	63 (19%); *n = 335*	0.08
Digoxin	82 (24%); *n = 347*	19 (5.7%); *n = 335*	<**0.01**
Antiarrhythmic drugs	82 (24%); *n = 347*	121 (36%); *n = 336*	<**0.01**

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium-channel blockers; CKD, chronic kidney disease; COBP, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EHRA, European Heart Rhythm Association; HE, haemorrhagic events; HF, heart failure; ICD, implantable cardioverter defibrillator; LA, left atrial; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonists; NA, non-applicable; NOAC, non-vitamin K antagonists oral anticoagulants; NT-proBNP, N-terminal fragments of B-type natriuretic peptide; PM, pacemaker; TE, thromboembolic events; VKA, vitamin K antagonists.

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Table 2 Characteristics of patients with atrial fibrillation depending on heart failure type

Variable	HFrEF (*n* = 168)	HFmrEF (*n* = 77)	HFpEF (*n* = 106)	*P*
Demographics				
Age, years	67 ± 11	68 ± 11	72 ± 8.9	<**0.01**
Female, *n* (%)	43 (26%)	25 (32%)	70 (66%)	<**0.01**
BMI, kg/m^2	29 ± 4.3; *n = 158*	30 ± 5.2; *n = 75*	29 ± 5.1; *n = 101*	0.66
Atrial fibrillation [*n* (%)]				
AF first diagnosed	9 (5.4%)	4 (5.2%)	5 (4.7%)	1.00
AF paroxysmal	33 (20%)	18 (23%)	25 (24%)	0.65
AF long-standing persistent	12 (7.1%)	17 (22%)	5 (4.7%)	<**0.01**
AF persistent	31 (18%)	11 (14%)	17 (16%)	0.71
AF permanent	83 (49%)	27 (35%)	54 (51%)	0.07
EHRA I	86 (51%)	30 (39%)	64 (60%)	**0.02**
EHRA II	41 (24%)	25 (32%)	20 (19%)	0.11
EHRA III-IV	41 (25%)	22 (29%)	22 (21%)	0.52
Concomitant diseases, *n* (%)				
Hypertension	98 (59%); *n = 167*	43 (57%); *n = 76*	61 (58%)	0.96
Coronary artery disease	86 (53%); *n = 161*	39 (55%); *n = 71*	33 (34%); *n = 98*	<**0.01**
NYHA III/IV	69 (41%)	27 (35%)	36 (34%)	0.44
Valvular disease	82 (51%); *n = 161*	35 (46%); *n = 76*	53 (50%)	0.53
Device therapy (PM/CRT/ICD)	54 (33%)	14 (18%)	22 (21%)	**0.03**
Dilated cardiomyopathy	45 (27%)	7 (9.1%)	2 (1.9%)	<**0.01**
Hypertrophic cardiomyopathy	5 (3.0%)	2 (2.6%)	5 (4.7%)	**0.74**
COPD	16 (9.6%); *n = 167*	6 (7.8%)	13 (12%)	0.66
CKD	40 (24%)	16 (21%)	22 (21%)	0.82
Diabetes mellitus	64 (38%); *n = 167*	29 (38%)	36 (34%)	0.77
Liver disease	10 (6.0%); *n = 167*	0 (0%)	2 (1.9%)	**0.04**
Smoking (current/former)	65 (40%); *n = 161*	24 (32%); *n = 75*	27 (27%); *n = 100*	0.08
Thromboembolic and bleeding risk, *n* (%)				
Previous TE	25 (15%); *n = 167*	12 (16%); *n = 76*	15 (14%)	0.96
Malignancy (current/former)	7 (4.2%)	2 (2.6%)	8 (7.8%) *n = 103*	0.30
CHA_2DS_2-VASc score	3.8 ± 1.7	3.8 ± 1.8	4.4 ± 1.5	**0.01**
Previous HE	16 (9.6%); *n = 167*	7 (9.1%)	15 (14%)	0.46
Anaemia	13 (7.7%)	5 (6.5%)	15 (14%)	0.15
Bleeding predisposition	16 (9.6%); *n = 167*	9 (12%)	6 (5.7%)	0.30
HAS-BLED score	1.8 ± 1.2	1.8 ± 1.2	1.7 ± 0.9	0.91
Electrocardiogram parameters				
Sinus rhythm	23 (14%)	19 (25%)	27 (25%)	**0.02**
AF/atrial flutter rhythm	123 (73%)	52 (67%)	71 (67%)	0.44
PM rhythm	22 (13%)	6 (7.8%)	8 (7.6%)	0.25
Heart rate, b.p.m.	84 ± 20; *n = 167*	79 ± 18	79 ± 16	0.15
PR interval [ms]	177 ± 51; *n = 22*	176 ± 32; *n = 18*	167 ± 45; *n = 26*	0.52
QRS complex [ms]	109 ± 25; *n = 130*	107 ± 26; *n = 69*	106 ± 29; *n = 95*	0.58
Bundle branch block, *n* (%)	35 (22%); *n = 157*	12 (16%); *n = 74*	18 (18%); *n = 102*	0.51
Echocardiography parameters				
LA, mm	50 ± 7.7; *n = 115*	48 ± 7.3; *n = 69*	49 ± 11; *n = 95*	0.10
LVDD, mm	61 ± 9.7; *n = 114*	54 ± 6.3; *n = 69*	49 ± 7.6; n = 95	<**0.01**
LVEF, %	28 ± 6.9; *n = 107*	44 ± 2.8; *n = 69*	56 ± 4.8; n = 95	<**0.01**
LVH, *n* (%)	23 (81%); *n = 131*	18 (23%); *n = 72*	36 (34%); *n = 106*	**0.01**
Laboratory parameters				
Haemoglobin, mg/dL	13.8 ± 1.8; *n = 160*	13.7 ± 1.8; *n = 74*	13.0 ± 1.7; *n = 99*	<**0.01**
Creatinine, mg/dL	1.2 ± 0.6; *n = 158*	1.1 ± 0.3; *n = 74*	1.1 ± 0.3; *n = 99*	0.37
NT-proBNP, pg/mL	4372 ± 4541; *n = 47*	3021 ± 4019; *n = 18*	2167 ± 2253; *n = 19*	0.05
Treatment [*n* (%)]				
VKA	101 (60%)	43 (56%)	57 (54%)	0.61
NOAC	45 (27%)	26 (34%)	36 (34%)	0.34
ACE inhibitors/ARBs	137 (82%); *n = 167*	61 (79%)	77 (74%); *n = 103*	**0.02**
Diuretics	132 (79%); *n = 167*	56 (73%)	72 (70%); *n = 103*	0.20
MRA	99 (59%); *n = 167*	37 (48%)	42 (41%); *n = 103*	**0.01**
Beta-blockers	149 (89%); *n = 167*	66 (86%)	85 (83%); *n = 103*	0.29
Non-dihydropyridine-CCB	5 (3.0%); *n = 167*	2 (2.6%)	4 (3.9%); *n = 103*	0.52
Dihydropyridine-CCB	26 (16%); *n = 167*	10 (13%)	11 (11%); *n = 103*	0.92
Digoxin	45 (27%); *n = 167*	16 (21%)	21 (20%); *n = 103*	0.40
Antiarrhythmic drugs	32 (19%); *n = 167*	24 (31%)	26 (25%); *n = 103*	0.11

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium-channel blockers; CKD, chronic kidney disease; COPP, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EHRA, European Heart Rhythm Association; ICD, implantable cardioverter defibrillator; HE, haemorrhagic events; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced preserved fraction; MRA, mineralocorticoid receptor antagonists; NOAC, non-vitamin K antagonists oral anticoagulants; NT-proBNP, N-terminal fragments of B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; VKA, vitamin K antagonists.

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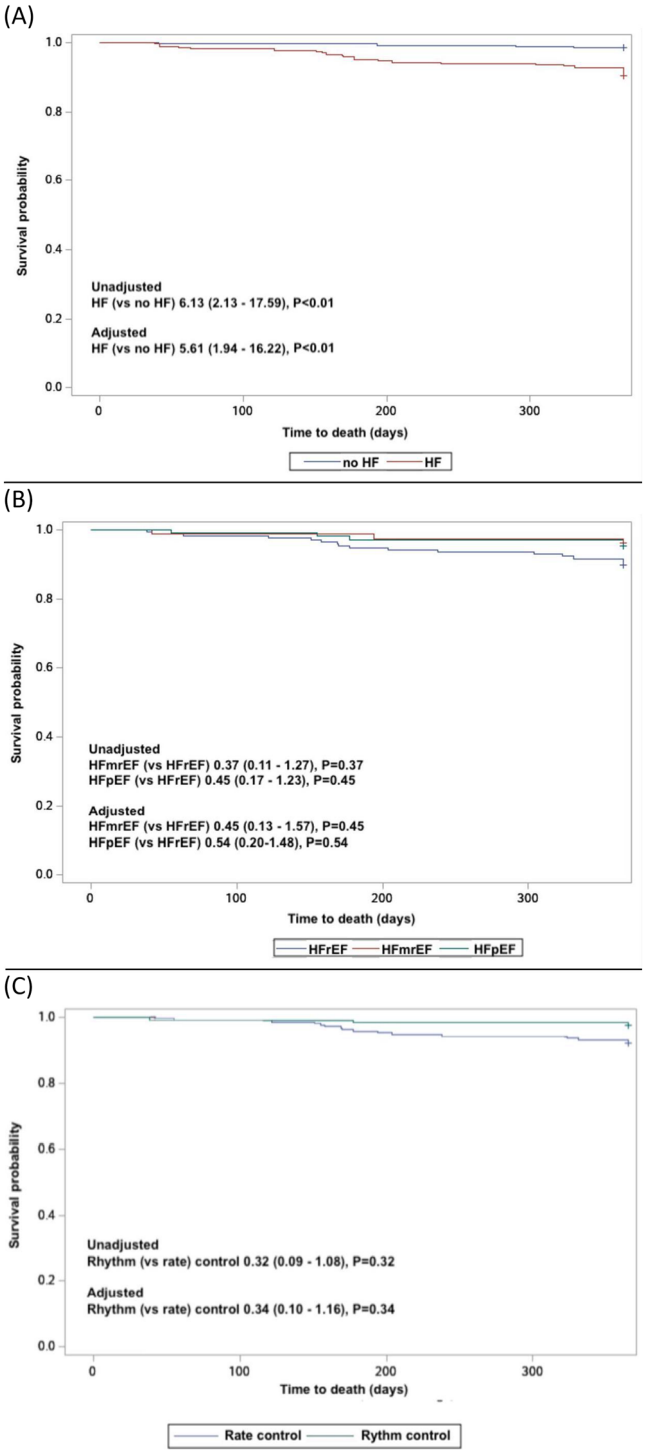
Table 3 Comparison of the rate and rhythm control treatment strategy among heart failure patients

Variable	Rate control (n = 202)	Rhythm control (n = 117)	P
Demographics			
Age, years	69 ± 11	68 ± 10	0.55
Female, *n* (%)	72 (36%)	53 (45%)	0.10
BMI, kg/m^2	29 ± 4.9; *n = 196*	29 ± 4.1; *n = 108*	0.43
AF, *n* (%)			
AF first detected	5 (2.5%)	10 (8.5%)	**0.02**
AF paroxysmal	9 (4.5%)	61 (52%)	<**0.01**
AF long-standing persistent	19 (9.4%)	13 (11%)	0.70
AF persistent	22 (11%)	27 (23%)	<**0.01**
EHRA, class I	120 (59%)	39 (33%)	<**0.01**
EHRA, class II	40 (20%)	40 (34%)	<**0.01**
EHRA III-IV	42 (21%)	38 (32%)	<**0.01**
Concomitant diseases [*n* (%)]			
Hypertension	119 (59%); *n = 201*	66 (57%); *n = 116*	0.72
CAD	90 (47%); *n = 190*	55 (50%); *n = 111*	0.72
NYHA III/IV	89 (44%)	26 (22%); *n = 117*	<**0.01**
Valvular heart disease	116 (59%); *n = 198*	38 (34%); *n = 113*	<**0.01**
Device therapy (PM/CRT/ICD)	65 (33%); *n = 199*	21 (18%); *n = 116*	<**0.01**
Dilated cardiomyopathy	35 (18%); *n = 200*	16 (14%); *n = 117*	0.37
Hypertrophic cardiomyopathy	9 (4.5%); *n = 200*	3 (2.6%); *n = 117*	0.38
COPD	24 (12%); *n = 202*	9 (7.7%); *n = 117*	0.26
CKD	45 (22%)	25 (21%)	0.89
Diabetes mellitus	78 (39%)	36 (35%); *n = 116*	0.18
Liver disease	10 (5.0%)	1 (0.9%)	0.06
Smoking (current/former)	69 (36%); *n = 192*	33 (30%); *n = 112*	0.26
Thromboembolic and bleeding risk, *n* (%)			
Previous TE	37 (19%); *n = 200*	12 (10%)	0.05
Malignancy (current/former)	9 (4.5%); *n = 200*	6 (5.2%); *n = 116*	0.79
CHA_2DS_2-VASc score	4.0 ± 1.7	3.9 ± 1.7	0.81
Previous HE	28 (14%)	5 (4.3%)	<**0.01**
Anaemia	19 (9.4%)	7 (6.0%)	0.40
Bleeding predisposition	21 (10%)	8 (6.8%)	0.32
HAS-BLED score	1.8 ± 1.1	1.7 ± 1.1	0.81
Electrocardiogram parameters			
Sinus rhythm	3 (1.5%)	61 (52%)	<**0.01**
AF/atrial flutter rhythm	172 (85%)	49 (42%)	<**0.01**
PM rhythm	27 (13%)	7 (6.0%)	0.73
Heart rate, b.p.m.	83 ± 17	78 ± 20	**0.01**
PR interval, ms	110 ± 0; *n = 2*	175 ± 43; *n = 64*	<**0.01**
QRS complex, ms	110 ± 24; *n = 163*	106 ± 29; *n = 129*	<**0.01**
Bundle branch block, *n* (%)	42 (22%); *n = 189*	16 (14%); *n = 114*	0.08
Echocardiography parameters			
LA, mm	51 ± 9.1; *n = 184*	46 ± 6.3; *n = 123*	<**0.01**
LVDD, mm	56 ± 10; *n = 184*	54 ± 8.5; *n = 123*	**0.02**
LVEF, %	40 ± 13; *n = 179*	45 ± 12; *n = 120*	0.32
LVH, *n* (%)	44 (24%); *n = 186*	24 (25%); *n = 97*	0.84
Laboratory parameters			
Haemoglobin, mg/dL	14 ± 1.7; *n = 192*	14 ± 1.9; *n = 139*	0.09
Creatinine, mg/dL	1.1 ± 0.3; *n = 191*	1.2 ± 0.7; *n = 138*	<**0.01**
NT-proBNP, pg/mL	3669 ± 3989; *n = 54*	3372 ± 4478; *n = 28*	0.46
Treatment [*n* (%)]			
VKA	125 (62%)	61 (52%)	0.10
NOAC	55 (27%)	43 (37%)	0.08
ACE inhibitors/ARBs	161 (80%)	88 (76%); *n = 116*	0.33
Diuretics	169 (84%)	68 (67%); *n = 116*	<**0.01**
MRA	123 (61%)	38 (33%); *n = 116*	<**0.01**

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium-channel blockers; CKD, chronic kidney disease; COBP, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EHRA, European Heart Rhythm Association; ICD, implantable cardioverter defibrillator; LA, left atrial; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonists; NOAC, non-vitamin K antagonists oral anticoagulants; NT-proBNP, N-terminal fragments of B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; VKA, vitamin K antagonists.

higher,[15,16] or lower[17,18] mortality rate in HFrEF comparing with HFmrEF or HFpEF. According to previously published analyses, the most important risk factors for reduced survival in HFrEF are coronary artery disease and liver dysfunction.[19] Similarly, in our study, patients with HFrEF had more often liver dysfunction as compared with those with HFmrEF and

Figure 1 Kaplan Meyer curves for all-cause death according to HF status *(A)*, HF type *(B)* and rhythm or rate control strategy within patients with HF *(C)*.



HFpEF (6.0% vs. 1.9%; $P = 0.04$) and coronary artery disease as compared with those with HFpEF (53% vs. 34%, $P < 0.01$).

Apart from anticoagulant therapy, the next consideration in a patient with AF and concomitant HF is the choice of rate or rhythm control strategies.[1] In our study we observed similar mortality rate between patients on rhythm and rate control. Those results are in line with recent Randomized ablation-based atrial fibrillation rhythm control versus rate

Table 4 Association of heart failure occurrence and long-term outcomes

Variable	HF (n = 351)	Without HF (n = 337)	P
Death	25 (7.1%)	4 (1.2%)	<**0.01**
Consent withdrawn/patient lost	88 (25%)	89 (26%)	0.73
Follow-up performed	238 (68%)	244 (72%)	0.21
Follow up			
CV interventions (PCI/PTCA/CABG/LAAO/valvular surgery/heart transplantation/other)	23 (10%); *n = 221*	13 (5.4%); *n = 240*	**0.046**
Hospital admission due to AF/AFL/AT	15 (6.8%); *n = 221*	34 (15%); *n = 231*	<**0.01**
Hospital admission due to CV events (HF new onset or worsening/device complications/arrhythmias other than AF/AFL/AT)	31 (14%)	17 (7.1%)	**0.02**
Thromboembolic events	3 (1.3%); *n = 223*	0 (0%); *n = 239*	0.07
Haemorrhagic events	4 (1.8%); *n = 223*	2 (0.8%); *n = 239*	0.37
Acute coronary syndrome	4 (1.8%); *n = 223*	2 (0.8%); *n = 239*	0.37
New onset CAD	10 (4.5%); *n = 221*	8 (3.4%); *n = 238*	0.49
New onset hypertension	12 (12%); *n = 97*	16 (16%); *n = 98*	0.43
New onset diabetes mellitus	9 (6.2%); *n = 146*	4 (2.1%); *n = 189*	0.06
New onset CKD	20 (9.0%); *n = 221*	5 (2.1%); *n = 235*	<**0.01**
Rhythm control interventions and device therapy during follow up			
Pharmacological cardioversion	7 (3.3%); *n = 215*	16 (7.0%); *n = 230*	0.08
Electrical cardioversion	10 (4.6%); *n = 216*	24 (10%); *n = 234*	**0.02**
AF catheter ablation	4 (1.9%); *n = 215*	9 (3.9%); *n = 233*	0.21
Device therapy (PM, ICD, and CRT)	11 (5.1%); *n = 216*	1 (0.4%); *n = 234*	**0.02**

AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter defibrillator; LAAO, left atrial appendage occlusion; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty.

Table 5 Association of heart failure type and long-term outcomes

Variable	HFrEF (n = 168)	HFmrEF (n = 77)	HFpEF (n = 106)	P
Death	17 (10%)	3 (3.9%)	5 (4.7%)	0.14
Consent withdrawn/patient lost	46 (27%)	16 (21%)	26 (25%)	0.56
Follow-up performed	105 (63%)	58 (75%)	75 (71%)	0.10
Follow up				
CV interventions (PCI/PTCA/CABG/LAAO/valvular surgery/heart transplantation/other)	9 (9.0%); *n = 100*	3 (5.5%); *n = 55*	11 (17%); *n = 66*	0.11
Hospital admission due to AF/AFL/AT	5 (5.0%); *n = 101*	6 (11%); *n = 54*	4 (6.1%); *n = 66*	0.34
Hospital admission due to CV events (HF new onset or worsening/device complications/arrhythmias other than AF/AFL/AT)	14 (14%)	6 (11%)	11 (17%)	0.64
Thromboembolic events	1 (1.0%)	1 (1.8%)	1 (1.5%)	0.91
Haemorrhagic events	1 (1.0%); *n = 101*	1 (1.8%); *n = 56*	2 (3.0%); *n = 66*	0.63
Acute coronary syndrome	2 (1.9%); *n = 101*	1 (1.8%); *n = 56*	1 (1.5%); *n = 66*	0.98
New onset CAD	6 (5.9%); *n = 101*	3 (5.5%); *n = 55*	1 (1.5%); *n = 65*	0.38
New onset hypertension	3 (7.7%); *n = 39*	4 (17%); *n = 23*	5 (14%); *n = 35*	0.49
New onset diabetes mellitus	4 (6.0%); *n = 67*	1 (2.9%); *n = 35*	4 (9.1%); *n = 44*	0.56
New onset CKD	14 (14%); *n = 100*	3 (5.4%); *n = 56*	3 (4.6%); *n = 65*	0.07
Rhythm control interventions and device therapy during follow up				
Pharmacological cardioversion	3 (3.1%); *n = 98*	3 (5.5%); *n = 55*	1 (1.6%); *n = 62*	0.55
Electrical cardioversion	6 (6.1%); *n = 99*	3 (5.5%); *n = 55*	1 (1.6%); *n = 62*	0.42
AF catheter ablation	2 (2.0%); *n = 98*	2 (3.6%); *n = 55*	0 (0%); *n = 62*	0.28
Device therapy (PM, ICD, and CRT)	6 (6.1%); *n = 99*	3 (5.5%); *n = 55*	2 (3.2%); *n = 62*	0.72

AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF; heart failure; ICD, implantable cardioverter defibrillator; LAAO, left atrial appendage occlusion; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty.

control trial in patients with heart failure and high burden atrial fibrillation (RAFT-AF) study, in which there was no statistical difference in all-cause mortality or HF events rates with ablation-based rhythm-control versus rate-control within patients with high burden AF and HF.[20] Also, based on systematic review with a total of 2486 patients with AF

Table 6 Association of rate and rhythm control management among heart failure patients and long-term outcomes

Variable	Rate control (n = 202)	Rhythm control (n = 102)	P
Death	16 (7.9%)	3 (2.6%)	0.05
Consent withdrawn/patient lost	50 (25%)	32 (27%)	0.61
Follow-up performed	136 (67%)	82 (70%)	0.61
Follow up			
CV interventions (PCI/PTCA/CABG/LAAO/valvular surgery/heart transplantation/other)	15 (12%); *n = 129*	6 (7.9%); *n = 76*	0.40
Hospital admission due to AF/AFL/AT	6 (4.7%); *n = 129*	6 (8.0%); *n = 75*	0.33
Hospital admission due to CV events (HF new onset or worsening/device complications/arrhythmias other than AF/AFL/AT)	3 (2.3%); *n = 130*	2 (2.6%); *n = 76*	0.88
Thromboembolic events	2 (1.5%); *n = 130*	1 (1.3%); *n = 76*	0.90
Haemorrhagic events	2 (1.5%); *n = 130*	2 (2.6%); *n = 76*	0.58
Acute coronary syndrome	2 (1.5%); *n = 130*	2 (2.6%); *n = 76*	0.58
New onset CAD	7 (5.4%); *n = 129*	3 (3.9%); *n = 76*	0.64
New onset hypertension	7 (14%); *n = 51*	4 (11%); *n = 36*	0.72
New onset diabetes mellitus	5 (6.2%); *n = 81*	4 (7.3%); *n = 55*	0.80
New onset CKD	8 (6.2%); *n = 129*	11 (15%); *n = 76*	**0.049**
Rhythm control interventions and device therapy during follow up			
Pharmacological cardioversion	1 (0.8%); *n = 130*	4 (5.5%); *n = 73*	**0.04**
Electrical cardioversion	4 (3.1%); *n = 130*	4 (5.4%); *n = 74*	0.43
AF catheter ablation	1 (0.8%); *n = 130*	3 (4.1%); *n = 73*	0.11
Device therapy (PM, ICD, and CRT)	4 (3.1%); *n = 130*	4 (5.4%); *n = 74*	0.43

AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF; heart failure; ICD, implantable cardioverter defibrillator; LAAO, left atrial appendage occlusion; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty.

and HF, mortality and stroke/TE rates were not significantly different in heart rate and rhythm control arms, whereas hospitalization rate was less frequent with heart rate control than with heart rhythm control.[21] In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[22] and Atrial Fibrillation and Congestive Heart Failure (AF-CHF)[23] trials, no differences were found between heart rate or rhythm control (predominantly pharmacologic) strategies in terms of mortality rate or frequency of cardiovascular complications. Nevertheless, some post-hoc analyses suggest superiority of sinus rhythm maintenance strategies, suggesting that people with HF with restored and maintained sinus rhythm have a better prognosis or improved physical performance.[24,25] Furthermore, the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) study showed that in highly selected patients with HF, AF ablation was associated with a significantly lower mortality rate for any cause or re-hospitalization rate due to worsening of HF compared with patients undergoing optimal pharmacological therapy.[26] A positive influence of catheter ablation on long-term outcomes in HF patients with AF have been shown.[27–29] Given that in most studies comparing rate versus drug-based rhythm control, the incidence of adverse outcomes was comparable in both strategies, whereas in the case of studies in which rate versus invasive-based rhythm control (e.g. ablation) was compared, this incidence was in favour of rhythm control strategy, it can be hypothesized that potential benefit of sinus-rhythm maintenance may have been neutralized by harmful effects of currently available antiarrhythmic therapies. Further randomized clinical trial are needed to provide more precise estimates in outcomes based on drug- or invasive-based rhythm control versus rate control strategies and to define whether one of these strategies is more likely to improve life quality.

Additional aspect that occurred in our study explaining why the rhythm control strategy did not reduce mortality rate among patients with HF, was that the power to detect a statistically significant result was diminished, as fewer events occurred in the study.

By showing no statistically significant difference in all-cause mortality, TE or HE between rate versus rhythm control strategies, it could be hypothesized that rate control could be considered a primary approach for patients with AF and HF in order to reduce hospitalisations and repeated cardioversion, hence hospital load, what is in line with previous studies.[22,23]

Limitations

The limitations of our study arise largely from the type of data (i.e. registry derived) analysed. First, there was a certain proportion of data missing for some of the patients. Second, the case report form enabled investigators to enter only data predefined by the coordinators of the registry. In terms of evaluation of diastolic function, those were limited to pulsed wave Doppler assessed parameters of mitral inflow. Regret-

fully, no data on other important indexes of diastolic function were gathered in the registry. Therefore, definitive verification of the pertinence of HFpEF diagnosis was not possible. Moreover, we were not able to assess how often each of those parameters is actually implemented in everyday clinical practice.

Conclusions

In our cohort of patients with AF, those with HF have a worse prognosis, with greater mortality and re-hospitalization rates due to CV events. No statistically significant difference in long-term outcomes among patients with HFrEF, HFmrEF, and HFpEF highlights the need to develop therapeutic strategies targeting functional status and survival for patients with HF and AF.

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Conflicts of interest

MB declares that she has no conflict of interest. MGa declares that she has no conflict of interest. PL has received a speaker honorarium from Bayer, Boehringer Ingelheim, and Pfizer. AT has received a speaker honorarium from Novartis and Boehringer Ingelheim. KO has received a speaker honorarium from Novartis, Boehringer Ingelheim, and Orion Pharma. MGr declares that he has no conflict of interest. MP declares that he has no conflict of interest. AW declares that she has no conflict of interest. MK declares that he has no conflict of interest. GO has received a speaker honorarium from Bayer, Boehringer Ingelheim, and Pfizer. RL declares that he has no conflict of interest. ZK declares that he has no conflict of interest. GYHL is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. PB has received a speaker honorarium from Bayer, Boehringer Ingelheim, and Pfizer.

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Supporting information

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

Table S1. Comparison between patients with heart failure with first detected AF vs persistent/permanent AF with regard to long-term outcomes and pharmacotherapy.

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