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ORIGINAL ARTICLE
Heart Failure

Relationships of Atrial Fibrillation at Diagnosis and Type of Atrial Fibrillation During Follow-up With Long-Term Outcomes for Heart Failure With Preserved Ejection Fraction

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Background: Few data are available regarding the impact of atrial fibrillation (AF) at diagnosis and type of AF during the follow-up period on long-term outcomes in patients with heart failure with preserved ejection fraction (HFpEF).

Methods and Results: In all, 1,697 patients diagnosed as HFpEF between March 2010 and December 2017 were included in this study. At enrollment, 698 (41.1%) patients had AF. Over a median follow-up of 1,017 days, there were no significant differences between patients with and without AF in the adjusted hazard ratio (HR) for all-cause death or admission for heart failure. However, those with AF had a higher risk of stroke (HR 1.831; P=0.003). Of 998 patients with sinus rhythm at enrollment, 139 (13.9%) developed new-onset AF. Predictors of new-onset AF were pulse, hemoglobin, left ventricular end-diastolic dimension, and B-type natriuretic peptide. Compared with sinus rhythm, paroxysmal AF had a similar risk for all-cause death, admission for HF, and stroke; persistent AF had a lower risk of all-cause death (HR 0.701; P=0.015), but a higher risk for admission for HF (HR 1.608; P=0.002); and new-onset AF had a lower risk for all-cause death (HR 0.654; P=0.040), but a higher risk of admission for HF (HR 2.475; P<0.001).

Conclusions: In patients with HFpEF, long-term outcome may differ by type of AF. Physicians need to consider individual risk with regard to AF type.

Key Words: Atrial fibrillation; Heart failure with preserved ejection fraction (HFpEF); Prognosis

Heart failure with preserved ejection fraction (HFpEF) is recognized worldwide as a different entity to heart failure that with reduced ejection fraction (HFrEF), and accounts for more than 50% of all heart failure patients. HFpEF can be complicated by atrial fibrillation (AF).[1] Although some patients maintain sinus rhythm throughout follow-up, others are found to experience various types of AF, including paroxysmal, persistent, and new-onset AF, during follow-up. However, few studies have comprehensively investigated AF in patients with HFpEF. Thus, the aims of this study were to investigate: (1) the incidence and long-term outcomes of AF at enrollment; (2) the incidence and determinants of new-onset AF; and (3) the relationship between AF type (paroxysmal, persistent, and new onset) and long-term outcome in patients with HFpEF.

Methods

Study Population

Patient data were extracted from the electronic medical records of Osaka University Hospital between March 1, 2010 and December 31, 2017. Patients were enrolled in the study if they had been diagnosed with chronic heart failure according to International Statisitical Classifications of Diseases (ICD)-10 codes, had B-type natriuretic peptide (BNP) concentrations ≥100 pg/mL, and an ejection fraction as assessed by echocardiography ≥50% and these measures had been obtained within 30 days of each other. Patients were excluded if they were aged ≤20 years, had acute coronary syndrome at enrollment, had severe valvular disease (e.g., aortic valve stenosis or regurgitation, mitral valve stenosis or regurgitation), hypertrophic cardiomyopathy,[2]

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Table 1. Patient Characteristics Stratified by the Presence or Absence of AF at Enrollment and During Follow-up

	Sinus rhythm (n=999)	AF present (n=698)	All (n=1,697)	P value
Baseline				
Age (years)	69.7±14.5	73.8±10.4	71.4±13.1	<0.001
Age ≥75 years (%)	45.6	50.7	47.7	0.040
Male sex (%)	47.9	59.2	52.6	<0.001
BMI (kg/m^2)	22.2±3.8	22.8±3.9	22.5±3.9	0.001
SBP (mmHg)	132±24	126±22	129±23	<0.001
DBP (mmHg)	70±14	69±14	69±14	0.134
Pulse (beats/min)	72±16	74±18	73±17	0.029
Diabetes (%)	47.5	44.4	46.3	0.215
Hypertension (%)	78.9	81.6	80	0.173
Dyslipidemia (%)	66	63.3	64.9	0.256
Current smoker (%)	39.8	42.2	40.8	0.331
Prior PCI (%)	51.4	56.6	53.1	0.315
Prior CABG (%)	22.6	25.9	23.7	0.459
History of stroke (%)	21.5	29.8	24.9	<0.001
History of HF admission (%)	25.9	34.4	29.3	<0.001
$CHADS_2$ score ≥2 (%)	82.4	84.4	83.2	0.278
Hemoglobin (g/dL)	11.7±2.1	12.4±2.3	12±2.2	<0.001
Hematocrit (%)	35.7±6.1	37.9±6.6	36.7±6.4	<0.001
Total cholesterol (mg/dL)	179±42	176±38	178±40	0.270
LDL-C (mg/dL)	100±31	97±29	99±30	0.117
HDL-C (mg/dL)	52±16	52±15	52±16	0.979
Triglyceride (mg/dL)	125±72	126±82	125±76	0.807
eGFR (mL/min/1.73 m^2)	53±30	52±22	53±27	0.496
CRP (mg/dL)	0.14 [0.04–0.71]	0.14 [0.04–0.73]	0.14 [0.05–0.64]	0.331
BNP (pg/mL)	179 [129–304]	192 [135–295]	185 [130–302]	0.438
LA diameter (mm)	40.2±7.5	48.2±10	43.5±9.4	<0.001
LVEDd (mm)	46.4±6.8	47.5±6.6	46.8±6.7	<0.001
LVESd (mm)	28.9±5.3	30±5.1	29.4±5.2	<0.001
Ejection fraction (%)	62.2±6.8	61±6.6	61.7±6.7	<0.001
TR pressure gradient (mmHg)	28±14	28±11	28±13	0.641
ACEI (%)	8.4	10.0	9.1	0.253
ARB (%)	27.8	28.7	28.2	0.710
ACEI or ARB (%)	35	39.1	36.7	0.086
β-blocker (%)	26.7	36.8	30.9	<0.001
Statin (%)	22.2	21.8	22.0	0.827
Loop diuretics (%)	30.5	38.3	33.7	0.001
Anti-arrhythmic drugs (%)	3.6	21.1	10.8	<0.001
Anticoagulation+antiplatelet (%)	1.0	9.3	4.4	<0.001
Antiplatelet (%)	32.7	26.5	30.2	0.006
Anticoagulation (%)	2.6	32.5	14.9	<0.001
Prior ablation (%)	1.3	1.0	1.2	0.575
During follow-up				
ACEI (%)	21.3	23.8	22.3	0.231
ARB (%)	56.1	56.3	56.2	0.919
ACEI or ARB (%)	63.7	68.1	65.5	0.061
β-blocker (%)	54.3	65.3	58.8	<0.001
Anticoagulation (%)	20.6	77.4	44.0	<0.001
Ablation (%)	4.2	5.4	4.7	0.236

Unless indicated otherwise, data are given as the mean±SD or median (interquartile range). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HF, heart failure; LA, left atrium; LDL-C, low density lipoprotein cholesterol; LVEDd, left ventricle end-diastolic diameter; LVESd, left ventricle end-systolic diameter; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TR, tricuspid regurgitation.

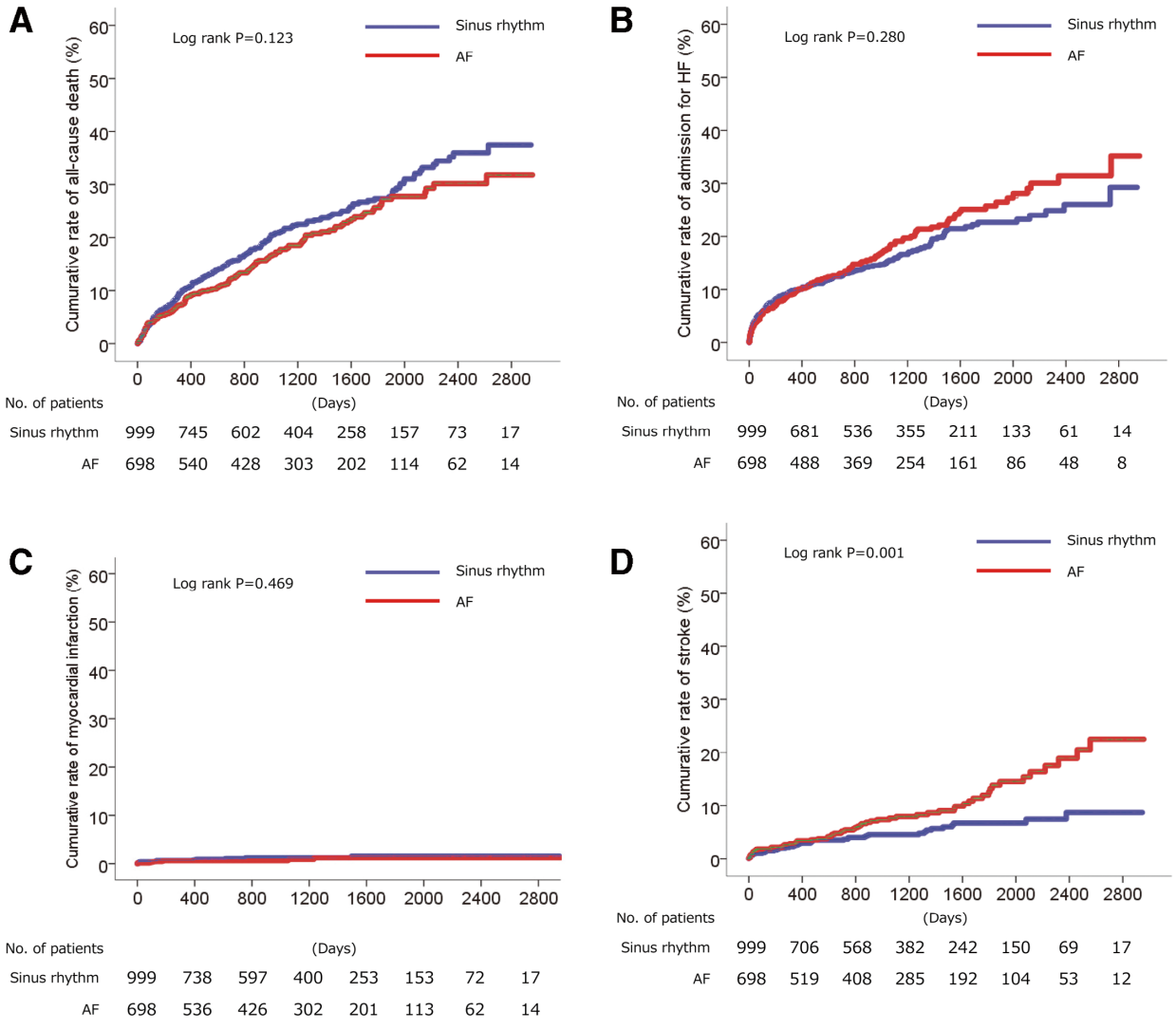

Figure 1. Kaplan-Meier curves of the cumulative incidence of (**A**) all-cause death, (**B**) admission for heart failure (HF), (**C**) myocardial infarction and (**D**) stroke stratified by sinus rhythm or atrial fibrillation (AF) at enrollment.

Table 2. Clinical Outcomes and Adjusted HRs for AF at Enrollment

	No. subjects	No. events (%)	Adjusted HR (95% CI)	P value
All cause death				
Sinus rhythm	999	219 (21.9)	Reference	
AF	697	134 (19.2)	0.852 (0.685–1.060)	0.150
Admission for HF				
Sinus rhythm	998	158 (15.8)	Reference	
AF	696	127 (18.2)	1.132 (0.892–1.438)	0.307
Myocardial infarction				
Sinus rhythm	998	12 (1.2)	Reference	
AF	696	6 (0.9)	0.635 (0.235–1.716)	0.371
Stroke				
Sinus rhythm	972	45 (4.6)	Reference	
AF	686	62 (9.0)	1.831 (1.233–2.717)	0.003

Hazard ratios (HRs) were adjusted for male sex, $CHADS_2$ score, the use of ACEI or ARB, β-blockers, statins, and loop diuretics, and BNP divided by 100. CI, confidence interval. Other abbreviations as in Table 1.

Table 3. Patient Characteristics Stratified by Sinus Rhythm and New Onset of AF Among Patients With Sinus Rhythm at Enrollment and During Follow-up

	Sinus rhythm (n=859)	New-onset AF (n=139)	All (n=998)	P value
Baseline				
Age (years)	69.4±15	72.1±10.1	69.7±14.5	0.007
Age ≥75 years (%)	45.9	44.6	45.7	0.782
Male sex (%)	47.7	48.9	47.9	0.794
BMI (kg/m^2)	22.2±3.8	22.6±3.8	22.2±3.8	0.171
SBP (mmHg)	131±24	133±22	132±24	0.300
DBP (mmHg)	70±14	69±12	70±14	0.315
Pulse (beats/min)	73±16	66±15	72±16	<0.001
Diabetes (%)	47.4	48.2	47.5	0.871
Hypertension (%)	78.3	82.7	78.9	0.237
Dyslipidemia (%)	65.7	68.6	66.1	0.500
Current smoker (%)	39.1	43.6	39.7	0.320
Prior PCI (%)	54.1	35	51.4	0.025
Prior CABG (%)	23.6	17.1	22.6	0.357
History of stroke (%)	20.5	27.3	21.5	0.070
History of HF admission (%)	26.8	20.4	25.9	0.116
$CHADS_2$ score ≥2 (%)	82.5	82.0	82.5	0.880
Hemoglobin (g/dL)	11.6±2.1	12.3±1.8	11.7±2.1	<0.001
Hematocrit (%)	35.5±6.2	37.4±5	35.7±6.1	<0.001
Total cholesterol (mg/dL)	177±43	187±33	179±42	0.059
LDL-C (mg/dL)	99±32	105±25	100±31	0.210
HDL-C (mg/dL)	52±16	54±17	52±16	0.389
Triglyceride (mg/dL)	124±72	128±73	125±72	0.688
eGFR (mL/min/1.73 m^2)	54±30	48±26	53±30	0.114
CRP (mg/dL)	0.15 [0.05–0.81]	0.09 [0.02–0.39]	0.14 [0.04–0.73]	0.678
BNP (pg/mL)	178 [128–299]	184 [130–403]	179 [129–304]	0.054
LA diameter (mm)	39.8±7.4	42.9±7.1	40.2±7.5	<0.001
LVEDd (mm)	46.1±6.7	47.9±7.2	46.4±6.8	0.003
LVESd (mm)	28.7±5.2	29.9±5.5	28.9±5.3	0.019
Ejection fraction (%)	62.2±6.8	62.1±6.9	62.2±6.8	0.890
TR pressure gradient (mmHg)	28±14	28±12	28±14	0.054
ACEI (%)	9.1	4.3	8.4	0.061
ARB (%)	27.4	30.9	27.9	0.383
ACEI or ARB (%)	34.9	36.0	35.1	0.810
β-blocker (%)	25.7	33.1	26.8	0.069
Statin (%)	22.2	22.3	22.2	0.986
Loop diuretics (%)	30.4	31.7	30.6	0.763
Anti-arrhythmic drugs (%)	3.1	6.5	3.6	0.051
Anticoagulation+antiplatelet (%)	1.0	0.7	1.0	0.718
Antiplatelet (%)	32.8	32.4	32.8	0.916
Anticoagulation (%)	2.7	2.2	2.6	0.721
Prior ablation (%)	1.4	0.7	1.3	0.513
During follow-up				
ACEI (%)	21.0	23.7	21.3	0.457
ARB (%)	55.2	61.9	56.1	0.140
ACEI or ARB (%)	63.1	67.6	63.7	0.303
β-blocker (%)	52.2	67.6	54.3	0.001
Anticoagulation (%)	15.4	53.2	20.6	<0.001
Ablation (%)	4.7	1.4	4.2	0.080

Unless indicated otherwise, data are given as the mean±SD or median (interquartile range). Abbreviations as in Table 1.

congenital heart disease, cardiac sarcoidosis, or amyloidosis, or had undergone heart transplantation.

The study protocol was approved by the Institutional Review Board of Osaka University Hospital. With regard to informed consent, the opt-out method was adopted.[3]

Data Collection

Patient demographics, electrocardiograms (ECG), laboratory data, echocardiograms, and medication data were collected from electronic medical records at Osaka University Hospital. AF was defined as documentation of AF on 12-lead ECG or Holter ECG during the follow-up period. Persistent AF was defined as AF observed throughout the entire follow-up period. Paroxysmal AF was defined as documented AF once and sinus rhythm observed on the latest ECG. New-onset AF was defined as sinus rhythm at enrollment and documented AF on the latest ECG. For follow-up data, Day 0 was set as the day when the inclusion criteria were fulfilled and the exclusion criteria were not met simultaneously. The clinical endpoint in this study was all-cause death, admission for heart failure, myocardial infarction, or stroke (defined as ischemic, lacunar, or hemorrhagic stroke), whichever occurred first.

Statistical Analysis

Continuous values are expressed as the mean±SD or as the median with the interquartile range if the distribution of data was skewed. Categorical data are presented as frequencies. Baseline characteristics between the groups were compared using t tests or repeated-measures analysis of variance for comparisons of continuous variables, and the Chi-squared or Fisher's exact test for categorical variables. Multivariate Cox regression analysis was used to identify factors associated with new-onset AF and to investigate the hazard ratio (HR) of AF at enrollment and each type of AF vs. sinus rhythm. Variables inserted into the models were variables that affected clinical outcomes. Outcomes data were described by the Kaplan-Meier method and compared by the log-rank test.

All analyses were performed using SPSS 23.0 (SPSS Japan, Tokyo, Japan). Statistical significance was defined as $P<0.05$ or a confidence interval (CI) that did not include 1.0.

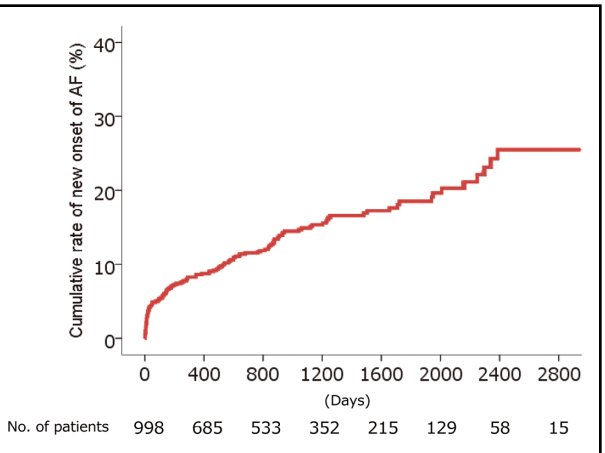

Figure 2. Kaplan-Meier curve of new-onset atrial fibrillation (AF) in heart failure with preserved ejection fraction patients in sinus rhythm at enrollment.

Results

Of the 1,845 patients who fulfilled the inclusion criteria for this study, 6 patients aged <20 years, 19 with acute coronary syndrome, 46 with congenital heart disease, 3 with cardiac amyloidosis, 6 with cardiac sarcoidosis, and 68 whose rhythm was unknown were excluded. This left 1,697 patients, with a mean age of 71.4 years, as study subjects.

At enrollment, the prevalence of AF was 41.1% (n=698). Patient characteristics stratified by the presence or absence of AF at enrollment are presented in **Table 1**. Patients with AF were more likely to be male, older, to have had a prior stroke, and experienced admission for heart failure. There were no significant differences in the prevalence of a $CHADS_2$ score ≥2 or in BNP concentrations between the 2 groups. Echocardiogram data revealed that patients with AF were more likely to have a larger left atrial and ventricular dimensions and to have a lower ejection fraction. In terms of medication at enrollment, patients with AF were more likely to be receiving β-blockers, diuretics, and

Table 4. Factors Associated With New Onset of AF by Multivariate Cox Regression Analysis

	Model 1			Model 2		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.007	0.989–1.025	0.435	–	–	–
Male sex	0.753	0.483–1.175	0.212	–	–	–
BMI	1.001	0.935–1.071	0.983	–	–	–
SBP	0.996	0.986–1.007	0.477	–	–	–
Pulse	0.974	0.958–0.991	0.003	0.974	0.958–0.990	0.002
Prior stroke	1.242	0.757–2.037	0.391	–	–	–
ACEI or ARB	0.756	0.477–1.200	0.235	–	–	–
Loop antidiuretics	0.957	0.564–1.623	0.869	–	–	–
Hemoglobin	1.200	1.058–1.362	0.005	1.172	1.043–1.317	0.008
LA dimension	1.029	0.992–1.068	0.126	1.032	0.997–1.068	0.078
LV end-diastolic dimension	1.060	1.021–1.100	0.002	1.045	1.010–1.082	0.013
TR pressure gradient	1.001	0.984–1.018	0.902	–	–	–
BNP divided by 100	1.088	1.035–1.144	0.001	1.089	1.045–1.136	<0.001

Model 1: forced entry method; Model 2, stepwise selection method. LV, left ventricle. Other abbreviations as in Tables 1,2.

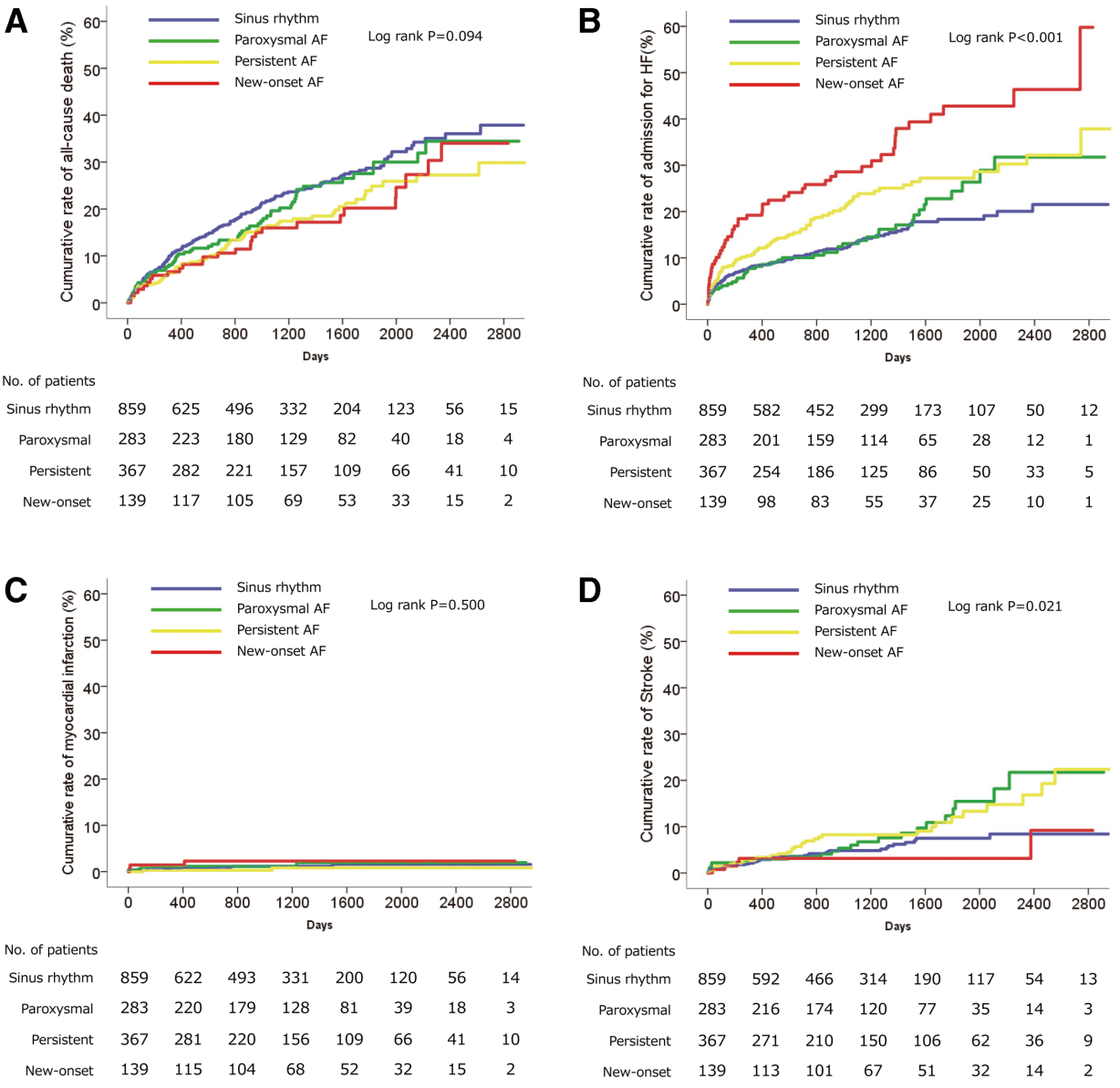

Figure 3. Kaplan-Meier curves of the cumulative incidence of (**A**) all-cause death, (**B**) admission for heart failure (HF), (**C**) myocardial infarction, and (**D**) stroke stratified by sinus rhythm, and paroxysmal, persistent and new-onset atrial fibrillation (AF).

anticoagulants. Over a median follow-up period of 1,017 days (IQR 411–1,661 days), there was no significant difference in the occurrence of all-cause death (**Figure 1A**), admission for heart failure (**Figure 1B**), myocardial infarction (**Figure 1C**), or stroke (**Figure 1D**) between the 2 groups. After adjustment for male sex, $CHADS_2$ score, the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), β-blockers, statins, loop diuretics, and BNP divided by 100, AF at enrollment was not associated with an increased risk of all-cause death, admission for HF, or myocardial infarction, but was associated with increased risk of stroke, with an adjusted HR of 1.831 (95% CI 1.233–2.717; P=0.003; **Table 2**). Although there was no significant difference in cardiac death between the 2 groups, non-cardiac death was significantly higher in AF than sinus group (P=0.043; **Supplementary Table 1**).

Among the 998 patients with sinus rhythm at enrollment, excluding 1 patient whose rhythm during the follow-up period was unknown, 139 (13.7%) patients developed new-onset AF during follow-up (**Table 3**; **Figure 2**). Patients with new-onset AF were more likely to be older and less likely to have received a previous percutaneous coronary intervention. Although there was no significant difference in anticoagulation treatment at enrollment between patients who maintained sinus rhythm and those who developed new-onset AF, the prevalence of anticoagulation therapy during the entire study period was significantly higher in patients with new-onset AF. On multivariate Cox regression analysis, pulse, hemoglobin, left ventricular end-diastolic

Table 5. Clinical Outcomes and Adjusted HR of Each Type of AF

	No. subjects	No. events (%)	Adjusted HR (95% CI)	P value
All-cause death				
Sinus rhythm	859	191 (22.2)	Reference	
Paroxysmal AF	282	62 (22.0)	0.948 (0.708–1.269)	0.718
Persistent AF	367	64 (17.4)	0.701 (0.525–0.934)	0.015
New-onset AF	139	28 (20.1)	0.654 (0.437–0.980)	0.040
Admission for HF				
Sinus rhythm	859	109 (12.7)	Reference	
Paroxysmal AF	281	44 (15.7)	1.207 (0.844–1.726)	0.303
Persistent AF	367	77 (21.0)	1.608 (1.191–2.171)	0.002
New-onset AF	139	49 (35.3)	2.475 (1.753–3.495)	<0.001
Myocardial infarction				
Sinus rhythm	859	9 (1.0)	Reference	
Paroxysmal AF	281	4 (1.4)	1.251 (0.376–4.162)	0.716
Persistent AF	367	2 (0.5)	0.398 (0.084–1.887)	0.246
New-onset AF	139	3 (2.2)	1.422 (0.347–5.827)	0.625
Stroke				
Sinus rhythm	835	40 (4.8)	Reference	
Paroxysmal AF	276	23 (8.3)	1.491 (0.881–2.522)	0.137
Persistent AF	362	33 (9.1)	1.582 (0.982–2.549)	0.059
New-onset AF	137	5 (3.6)	0.555 (0.214–1.439)	0.226

HRs were adjusted for male sex, $CHADS_2$ score, the use of ACEI or ARB, β-blockers, statins, and loop diuretics, and BNP divided by 100. Abbreviations as in Tables 1,2.

dimension, and BNP divided by 100 were extracted as factors associated with the occurrence of new-onset AF in the current population (**Table 4**, Model 1). These factors remained unchanged when a stepwise selection method was used (**Table 4**, Model 2).

Among the 1,648 patients for whom rhythm data were available during the follow-up period, 859 (52.1%), 283 (17.2%), 367 (22.3%), and 139 (8.4%) had sinus rhythm, paroxysmal AF, persistent AF, and new-onset AF, respectively (**Supplementary Table 2**). Although there was no significant difference in all-cause death among the 4 groups (**Figure 3A**), there was a significant difference among the groups in admission for heart failure (**Figure 3B**). In addition, although there was no significant difference in myocardial infarction among the groups (**Figure 3C**), the incidence of stroke differed (**Figure 3D**). **Table 5** shows clinical events during follow-up and the adjusted HR for each type of AF when the HR for sinus rhythm was set at a reference value of 1. There was no significant risk difference in all cause-death, admission for HF, myocardial infarction, or stroke between sinus rhythm and paroxysmal AF. Although persistent AF had lower risk for all-cause death, it had higher risk for admission for HF and tended to have a higher risk for stroke. Furthermore, although new-onset AF had lower risk for all-cause death, it had a higher risk for admission for HF and no significant difference in myocardial infarction or stroke. These results suggest that the effect on clinical outcome differed for each type of AF. With regard to cause of death, there was no significant difference in cardiac death among the 4 groups (P=0.094). However, there was a significant difference in non-cardiac deaths among the 4 groups (P=0.010), with a lower rate of non-cardiac deaths in the persistent AF than sinus group (P=0.002; **Supplementary Table 3**).

Discussion

We retrospectively investigated the prevalence, characteristics, and outcomes of HFpEF complicated with AF at enrollment, as well as the type of AF that occurred during follow-up.

The incidence of AF at enrollment was 41.4%. Previous reports of HFpEF have reported a prevalence of AF ranging from 19% in a randomized controlled trial[5] to 65% in an observational study.[6] The occurrence of AF has been associated with age and diastolic function, which is impaired with advanced age.[7,8] Therefore, the prevalence of AF in HFpEF appears to increase with age.[5,6,9,10]

The incidence of new-onset AF during a median follow-up period of approximately 1,000 days in the present study was 13.9%. In contrast, the incidence of new-onset AF in a community-based study with a follow-up period of 3.7 years and in the TOPCAT trial, which examined the efficacy of spironolactone with a follow-up period of 3.1 years, was 31.6%[11] and 5%,[12] respectively. Compared with patients enrolled in randomized studies, patients registered in observational studies are generally more likely to be older and to have higher morbidity. Accordingly, the incidence of new AF may be higher in the present study than in randomized studies. To date, however, few reports have examined factors associated with the determinants of new-onset AF in patients with HFpEF. In their substudy of the TOPCAT trial, Neefs et al showed that spironolactone, ACEI, ARBs, and β-blockers were not associated with a reduced risk of new-onset AF.[12] In contrast, in the present study we found that pulse (bradycardia), elevated hemoglobin, enlarged left ventricular end-diastolic dimension, and elevated BNP were associated with an increased risk of new-onset AF. Among cardiac factors,

left ventricular overload and impaired sinus node function may have the potential to induce new-onset AF, whereas elevated hemoglobin was extracted as an extracardiac factor for new-onset AF. We occasionally experience elevated hemoglobin in patients with paroxysmal AF in clinical practice.[13] One reason for this may be polyuria induced by excess secretion of atrial natriuretic peptide.[14] Although no previous reports have described an association between elevated hemoglobin and new-onset AF, sleep apnea syndrome, which induces an increase hemoglobin levels due to hypoxia, could lead to this phenomenon. Further studies are needed to confirm this observation and clarify the mechanism of this relationship.

Findings to date on AF and outcomes in patients with HFpEF are inconsistent. AF was shown to confer a higher risk of all-cause death in some reports,[6,11,15] but not in another study.[16] In the present study, although we saw no significant difference in all-cause death or admissions for HF and myocardial infarction between AF at enrollment and sinus rhythm, AF at enrollment carried a higher risk of stroke than sinus rhythm. When we compared the cause of death between the 2 groups in the present study (**Supplementary Table 1**), we found no significant difference in cardiac deaths (2.8% vs 3.2%; P=0.797), but did find that non-cardiac deaths were significantly higher in patients with sinus rhythm than in those with AF (15.9% vs 12.6%; P=0.043). The higher rate of non-cardiac deaths in our patients with sinus rhythm may have been diminished by the difference in the risk of all-cause death between the 2 groups.

We further divided patients by type of rhythm during follow-up. Compared with sinus rhythm, used as the reference group, persistent AF was associated with a lower risk of all-cause death. We acknowledge that the study design prevents us from identifying any cause-effect relationship, and we are unable to propose a mechanism by which persistent AF was associated with a lower rate of all-cause deaths. Nevertheless, we speculate that one possibility is associated with the lower rate of non-cardiac deaths in patients with persistent AF compared with those with sinus rhythm (10.1% vs. 16.4%; P=0.002; **Supplementary Table 3**). A second possibility may be the recent progress made in the use of β-blockers to control heart rate, which has shown beneficial effects in patients with heart failure.[17–20] This may have attenuated the risk of all-cause death in patients with AF vs. those with sinus rhythm. Indeed, there was no significant difference in cardiac deaths among the 4 groups (P=0.684). Conversely, patients with persistent AF and new-onset AF had a significantly higher risk of admission for HF. Again, although we are unable to propose a cause-and-effect relationship between new-onset AF and admission for HF, we propose 2 possibilities: first, new-onset AF could result in admission for HF; second, worsening of HF requiring admission could induce new-onset AF. Although the type of AF was not associated with an increased risk of stroke, the HR was >1.0 in paroxysmal and persistent AF but <1.0 in new-onset of AF, indicating that the risk of stroke may differ among types of AF. Importantly, we consider that these findings mandate the need for careful consideration and treatment of patients based on their individual risk according to type of AF. In addition, similar outcomes were observed when we excluded patients who underwent catheter ablation for AF during follow-up (data not shown).

The Japan Circulation Society guideline recommends dabigatran and apixaban for anticoagulation in patients with AF, and rivaroxaban, edoxiaban, and warfarin in patients with a $CHADS_2$ score ≥1.[21] In the present study, we included patients with heart failure, indicating a $CHADS_2$ score ≥1. Despite the fact that the use of anticoagulation therapy during follow-up was relatively low (43.8%, 58.9%, and 7.9% in paroxysmal, persistent, and new-onset of AF, respectively; **Supplementary Table 2**), care in clinical practice settings should consider a prescription for anticoagulation in patients with HFpEF complicated with AF, if not contraindicated.

This study had several limitations. First, it was a retrospective analysis conducted at a single center, leading to the possibility of bias. Second, our definition of HFpEF differed from that in other studies: we defined HFpEF as both elevated BNP ≥100 pg/mL and an ejection fraction assessed by echocardiography of ≥50%. Other studies have defined HFpEF using the Framingham criteria,[22,23] ICD-9 codes,[24,25] physicians' discretion,[6,15] or an ejection fraction of ≥40%[26,27] or 45%.[12,24,25,28] This difference in the definition of HFpEF among studies must be recognized. Third, it may be possible that we missed paroxysmal AF in the sinus rhythm group. Indeed, 2.6% of patients in that group received anticoagulation at enrollment. Fourth, due to a lack of data on bleeding history, we did not calculate the ORBIT bleeding score.[29] Fifth, we need to recognize the lower prescription rate of anticoagulant drugs than we expected during the study period in our study population. Therefore, physicians must exercise caution if they use our data in clinical practice.

In conclusion, this retrospective analysis of HFpEF showed that the prevalence of AF at enrollment and any type of AF during follow-up was relatively high, at 41.1% and 47.9%, respectively. New-onset AF was observed in 13.9% of patients. Factors associated with an increased risk of new-onset AF were pulse (bradycardia), elevated hemoglobin, enlarged left ventricular end-diastolic dimension, and elevated BNP. Although there was no significant difference in all-cause deaths between patients with AF at enrollment and those in sinus rhythm, the risk of all-cause death and admission for HF differed between the sinus rhythm group and different types of AF during the follow-up period. Therefore, physicians should approach the care of these patients based on individual risk according to type of AF.

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IRB Information

This study was approved by the Osaka University Research Ethics Committee (Reference no. 16515).

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Supplementary Files

Please find supplementary file(s);
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