Age-Dependent Prognostic Impact of Paroxysmal Versus Sustained Atrial Fibrillation on the Incidence of Cardiac Death and Heart Failure Hospitalization (the Fushimi AF Registry)

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Data regarding the relation of the type of atrial fibrillation (AF) to the incidence of cardiac events remain scarce. This study sought to investigate the association of AF type with the incidences of cardiac death and heart failure (HF) hospitalization between paroxysmal and sustained (persistent/permanent) AF in the overall population and in age subgroups (≤74, 75 to 84, and ≥85 years), using the data from a Japanese community-based prospective survey, the Fushimi AF Registry. The participants started to be enrolled since March 2011, and follow-up data were available for 4,304 patients by the end of November 2017. Patients with sustained AF (n = 2,187, 50.8%) had more co-morbidities with higher mean CHA_2DS_2-VASc score than those with paroxysmal AF (n = 2,117, 49.2%) (sustained vs paroxysmal: 3.57 ± 1.69 vs 3.17 ± 1.67, p <0.001). During a median follow-up of 1,307 (interquartile range: 709 to 2,156) days, the composite of cardiac death and HF hospitalization occurred more frequently in those with sustained AF (event rate: 5.1 vs 2.8 per 100 person-years; p <0.001). On multivariate analysis, sustained AF was independently associated with higher incidence of this composite end point (adjusted hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.12 to 1.63, p = 0.002). In age subgroups, this association was observed only in the younger AF patients (≤74 years) (adjusted HR: 2.03, 95% CI: 1.44 to 2.86, p <0.001), but not in the older subgroups (p = 0.018 for interaction). In conclusion, sustained AF was associated with higher incidence of the composite of cardiac death and HF hospitalization than paroxysmal AF, with different relations seen depending on age subgroups. **(Am J Cardiol 2019;124:1420−1429)**

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases the risks of ischemic stroke and death. Several studies have shown higher risks of sustained (persistent/permanent) AF for both thromboembolism and all-cause mortality, compared with paroxysmal AF.[1−4] Heart failure (HF) has been focused as a main cause of cardiovascular (CV) death in AF patients.[5−8] In the Framingham Heart Study,[9] the subsequent development of HF was associated with about threefold increased mortality in AF patients. However, there are limited data regarding how differently AF type affects HF worsening, depending on the age of each patient, especially in Asian cohorts where the burden of AF is greatly increasing due to an aging society.[10] The objective of this study was to examine the prognostic impacts of paroxysmal versus sustained AF on cardiac death and HF hospitalization, and its differences among age subgroups, in a community-based cohort of Japanese AF patients.

Methods

The detailed study design, patient enrollment, the definition of the measurements, and the subjects' baseline clinical characteristics of the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834).[11] The inclusion criterion for the registry is the documentation of AF on a 12-lead electrocardiogram or Holter monitoring at any time. There were no exclusion criteria. A total of 81 institutions participated in the registry of Fushimi district, Kyoto, Japan

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See page 1428 for disclosure information.

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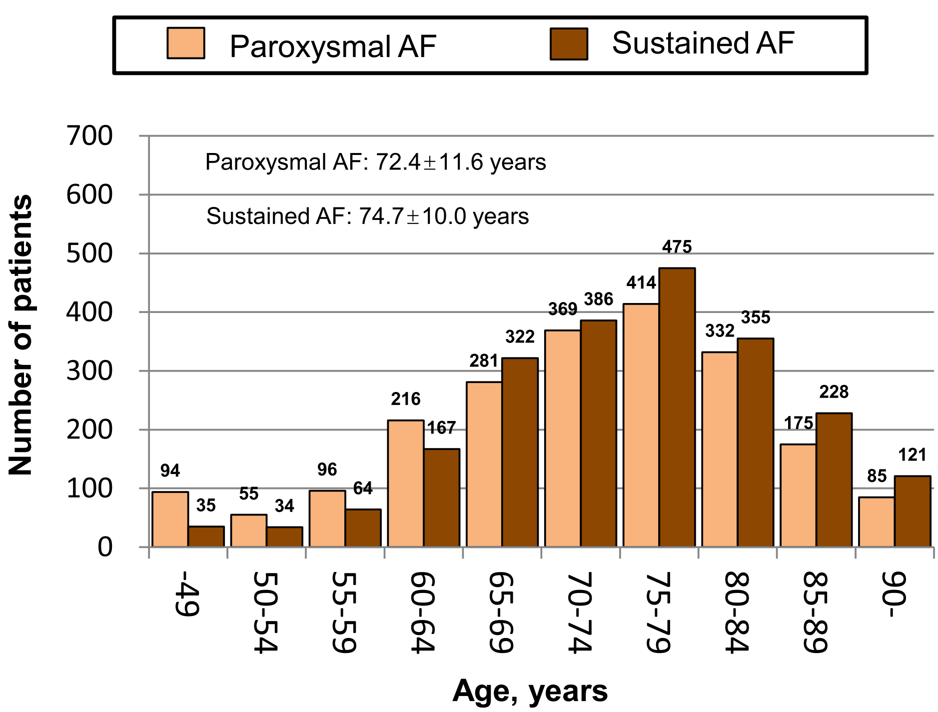
(e-Appendix). We started to enroll patients from March 2011. Collection of follow-up information was mainly conducted through review of the inpatient and outpatient medical records, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by mail or telephone. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

Type of AF was defined as the followings in accordance with the 2019 AHA/ACC/HRS and 2016 ESC guidelines for the management of patients with AF[12,13]: paroxysmal AF was defined as self-terminating AF within 7 days; persistent AF was defined as AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more; and permanent AF was defined as AF that is accepted by the patient (and physician). Because distinguishing persistent and permanent type is sometimes difficult in daily clinical practice, we combined these 2 subtypes as sustained AF, as described in our previous reports.[4,14] Next, we compared baseline clinical characteristics and outcomes between paroxysmal AF and sustained AF, not only in the entire cohort but also among the 3 groups by age (≤74 years, 75 to 84 years, and ≥85 years), as previously reported.[15]

The definition of pre-existing HF used in this study was having one of the following at enrollment: (1) history of hospitalization for HF before the enrollment, (2) symptomatic HF (New York Heart Association class ≥2), or (3) decreased left ventricular ejection fraction (<40%). Anemia was defined according to the World Health Organization criteria (hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women). Renal dysfunction was diagnosed as the estimated glomerular filtration rate (eGFR) <60 mL/min/m^2 at baseline. Oral anticoagulant (OAC) included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Antiplatelet drugs included aspirin, clopidogrel, ticlopidine, and cilostazol. OAC and antiplatelet drug usage were based on the prescription data at enrollment.

The primary end point in the analysis was the composite of cardiac death and HF hospitalization during the follow-up period. Causes of death including cardiac death due to HF, acute coronary syndrome, or dysrhythmia were adjudicated after consideration of all the available information as reported previously.[8] Admission for HF was determined by the attending physician based on history, clinical presentation (symptoms and physical examination), response to HF therapy, chest radiography, echocardiography, cardiac catheterization findings, and in-hospital course.

Continuous variables were expressed as mean ± standard deviation, or median and interquartile range according to the distributions and compared using Student's *t* test or Wilcoxon rank-sum test on the basis of the distribution.



	≤74 years	75-84 years	≥85 years	Overall
Paroxysmal AF	1,111 (52%)	746 (35%)	260 (12%)	2,117 (100%)
Sustained AF	1,008 (46%)	830 (38%)	349 (16%)	2,187 (100%)

Figure 1. The distributions of age between paroxysmal and sustained AF groups in the overall population. AF = atrial fibrillation

Table 1
Baseline characteristics, co-morbidities, and prescription in patients with paroxysmal AF versus with sustained AF across age groups

Variable	Overall			≤74 years			75 to 84 years			≥85 years		
	Paroxysmal AF (n = 2,117)	Sustained AF (n = 2,187)	p Value	Paroxysmal AF (n = 1,111)	Sustained AF (n = 1,008)	p Value	Paroxysmal AF (n = 746)	Sustained AF (n = 830)	p Value	Paroxysmal AF (n = 260)	Sustained AF (n = 349)	p value
Age (y)	72.4 ± 11.6	74.7 ± 10.0	<0.001	67 (61, 71)	68 (63, 71)	<0.001	79 (77, 81)	79 (77, 81)	0.70	88 (86, 91)	88 (86, 90)	0.12
Female	890 (42%)	847 (39%)	0.026	377 (24%)	375 (37%)	<0.001	338 (45%)	348 (41%)	0.18	175 (67%)	224 (64%)	0.42
BMI (kg/m^2)	23.0 ± 3.9	23.3 ± 4.2	0.014	23.7 ± 3.8	24.1 ± 4.6	0.041	22.5 ± 3.7	23.1 ± 3.7	0.002	21.2 ± 3.8	21.5 ± 3.7	0.19
Prior catheter ablation	181 (9%)	93 (4%)	<0.001	123 (11%)	71 (7%)	0.001	53 (7%)	18 (2%)	<0.001	5 (2%)	4 (1%)	0.43
Estimated GFR (mL/min)	61.7 (48.0, 75.9)	59.3 (46.8, 71.2)	<0.001	68.0 (54.6, 81.7)	63.9 (52.1, 75.6)	<0.001	56.2 (44.2, 68.1)	57.6 (46.0, 68.8)	0.28	50.3 (37.0, 64.6)	47.8 (35.9, 61.1)	0.13
$CHADS_2$ score	1.83 ± 1.28	2.22 ± 1.36	<0.001	1.22 ± 1.07	1.51 ± 1.15	<0.001	2.44 ± 1.13	2.76 ± 1.20	<0.001	2.74 ± 1.12	2.99 ± 1.23	0.010
CHA_2DS_2-VASc score	3.17 ± 1.67	3.57 ± 1.69	<0.001	2.24 ± 1.42	2.56 ± 1.43	<0.001	4.05 ± 1.26	4.29 ± 1.38	<0.001	4.59 ± 1.29	4.75 ± 1.39	0.073
Previous stroke/TIA	305 (14%)	473 (22%)	<0.001	130 (12%)	170 (17%)	<0.001	111 (15%)	193 (23%)	<0.001	64 (25%)	110 (32%)	0.062
Pre-existing heart failure	379 (18%)	791 (36%)	<0.001	135 (12%)	290 (29%)	<0.001	155 (21%)	322 (39%)	<0.001	89 (34%)	179 (51%)	<0.001
Valvular heart disease	251 (12%)	488 (22%)	<0.001	99 (9%)	170 (17%)	<0.001	107 (14%)	210 (25%)	<0.001	45 (17%)	108 (31%)	<0.001
Cardiomyopathy	49 (2%)	71 (3%)	<0.001	28 (3%)	44 (4%)	0.019	15 (2%)	25 (3%)	0.21	6 (2%)	2 (0.5%)	0.063
Hypertension	1,354 (64%)	1,353 (62%)	0.16	672 (60%)	606 (60%)	0.86	501 (67%)	539 (65%)	0.35	181 (70%)	208 (60%)	0.011
Diabetes mellitus	493 (23%)	520 (24%)	0.70	265 (24%)	253 (25%)	0.50	174 (23%)	195 (23%)	0.94	54 (21%)	72 (21%)	0.91
Dyslipidemia	1,042 (49%)	853 (39%)	<0.001	550 (50%)	442 (44%)	0.009	385 (52%)	313 (38%)	<0.001	107 (41%)	98 (28%)	<0.001
Coronary artery disease	347 (16%)	285 (13%)	0.002	142 (13%)	102 (10%)	0.055	146 (20%)	137 (17%)	0.11	59 (23%)	46 (13%)	0.002
Prior myocardial infarction	162 (8%)	99 (5%)	<0.001	66 (6%)	32 (3%)	0.002	68 (9%)	45 (5%)	0.005	28 (11%)	22 (6%)	0.047
Peripheral artery disease	93 (4%)	84 (4%)	0.36	34 (3%)	31 (3%)	0.98	43 (6%)	39 (5%)	0.34	16 (6%)	14 (4%)	0.23
Renal dysfunction	925 (47%)	1,075 (52%)	0.002	340 (34%)	376 (40%)	0.004	414 (58%)	450 (57%)	0.52	171 (68%)	249 (73%)	0.18
Chronic obstructive pulmonary disease	95 (4%)	129 (6%)	0.037	39 (4%)	54 (5%)	0.039	45 (6%)	54 (7%)	0.70	11 (4%)	21 (6%)	0.33
Anemia	771 (39%)	727 (35%)	0.009	256 (25%)	200 (21%)	0.035	342 (48%)	313 (39%)	<0.001	173 (69%)	214 (64%)	0.17
Prescription at baseline												
Oral anticoagulant	918 (43%)	1,460 (67%)	<0.001	461 (41%)	678 (67%)	<0.001	378 (51%)	601 (72%)	<0.001	79 (30%)	181 (52%)	<0.001
Warfarin	643 (30%)	1,172 (54%)	<0.001	312 (28%)	525 (52%)	<0.001	274 (37%)	495 (60%)	<0.001	57 (22%)	152 (44%)	<0.001
NOAC	275 (13%)	288 (13%)	0.86	149 (13%)	153 (15%)	0.24	104 (14%)	106 (13%)	0.50	22 (8%)	29 (8%)	0.95
Antiplatelet drug	590 (28%)	590 (27%)	0.51	252 (23%)	236 (23%)	0.69	240 (32%)	244 (29%)	0.23	98 (38%)	110 (32%)	0.11
Diuretics	447 (21%)	778 (36%)	<0.001	169 (15%)	289 (29%)	<0.001	183 (25%)	317 (38%)	<0.001	95 (37%)	172 (49%)	0.002
ACE-I/ARBs	914 (43%)	999 (46%)	0.10	454 (41%)	452 (45%)	0.065	339 (45%)	396 (48%)	0.36	121 (47%)	151 (43%)	0.42
Digitalis	109 (5%)	378 (17%)	<0.001	44 (4%)	170 (17%)	<0.001	44 (6%)	156 (18%)	<0.001	21 (8%)	52 (15%)	0.010
Beta-blocker	595 (28%)	713 (32%)	0.001	312 (28%)	376 (37%)	<0.001	217 (29%)	251 (30%)	0.61	66 (25%)	86 (25%)	0.83
Antiarrhythmic drugs	653 (31%)	191 (9%)	<0.001	386 (34%)	113 (11%)	<0.001	217 (29%)	60 (7%)	<0.001	50 (19%)	18 (5%)	<0.001
Statins	560 (26%)	488 (22%)	0.002	277 (25%)	242 (24%)	0.62	218 (29%)	194 (23%)	0.008	65 (25%)	52 (15%)	0.002

AF = atrial fibrillation; BP = blood pressure; NOAC = nonvitamin K oral anticoagulant; Renal dysfunction: estimated glomerular filtration rate <60 mL/min/m^2, TIA = transient ischemic attack.

Categorical data are presented as number (%). Continuous data are presented as mean ± standard deviation (SD), or median and interquartile range (25%, 75%) according to the distribution. Anemia was defined according to the World Health Organization criteria (hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women).

Categorical variables are presented as numbers and percentages and compared using the chi-square test when appropriate; otherwise, we used Fisher's exact test. The cumulative incidences of clinical outcomes were estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test. We carried out a multivariate analysis for the indicators of cardiac death, HF hospitalization, and the composite of these events using the Cox proportional hazards model. The covariates chosen to be included were age (per 10 years for overall analysis, and not included for each age subgroup analysis), female (vs male), body mass index as the 3 categorical variable (<18.5 kg/m^2, 18.5 to <25.0 kg/m^2, ≥25.0 kg/m^2), sustained AF (vs paroxysmal AF), pre-existing HF, hypertension, diabetes mellitus, previous stroke or transient ischemic attack (TIA), peripheral artery disease, previous myocardial infarction, anemia, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, and renal dysfunction at baseline. p value for interaction was also assessed to examine heterogeneity in subgroups of the prespecified factors. In addition, a selection impact analysis was performed, describing the hazard ratios (HR) of sustained AF (vs paroxysmal AF) in the younger population under different age-based thresholds for the incidence of the primary end point. We used JMP version 14 (SAS Institute, Cary, NC) to perform all of these analyses. Two-sided p values less than 0.05 were considered statistically significant.

Results

Of 4,760 patients who were enrolled by the end of November 2016, follow-up data (collected annually) were available for 4,325 patients as of November 2017 (follow-up rate: 90.9%). Of these 4,325 patients, 21 patients were excluded because their baseline prescription data were unavailable. Finally, among 4,304 patients, 2,117 had paroxysmal AF and 2,187 had sustained AF at enrollment of our registry. The median follow-up period was 1,307 (interquartile range: 709 to 2,156) days.

The age distribution of paroxysmal and sustained AF groups in the entire cohort is shown in Figure 1. The proportion of sustained AF in each 5-year age subgroup increased as age became older, and accounted for more than a half at the age of ≥65 years. Baseline clinical characteristics of patients with paroxysmal AF and sustained AF in the overall population and age subgroups are summarized in Table 1. The history of stroke or TIA and the prevalence of pre-existing HF were higher in sustained AF than in paroxysmal AF group with a higher CHA_2DS_2-VASc score, irrespective of age subgroups. The prevalence of anemia and the history of myocardial infarction were lower in sustained AF in the overall population. These differences were consistent among every age subgroup except for anemia at age of ≥85 years. As for medication, OAC, diuretics, and digitalis were prescribed more frequently in sustained AF than in paroxysmal AF group, irrespective of age subgroups. Beta-blockers were prescribed more frequently in sustained AF group at the age of ≤74 years, but similarly between the 2 groups among the other older age groups (75 to 84 years and ≥85 years). Antiarrhythmic drugs were prescribed less frequently as age became older, and less frequently in sustained AF than in paroxysmal AF group.

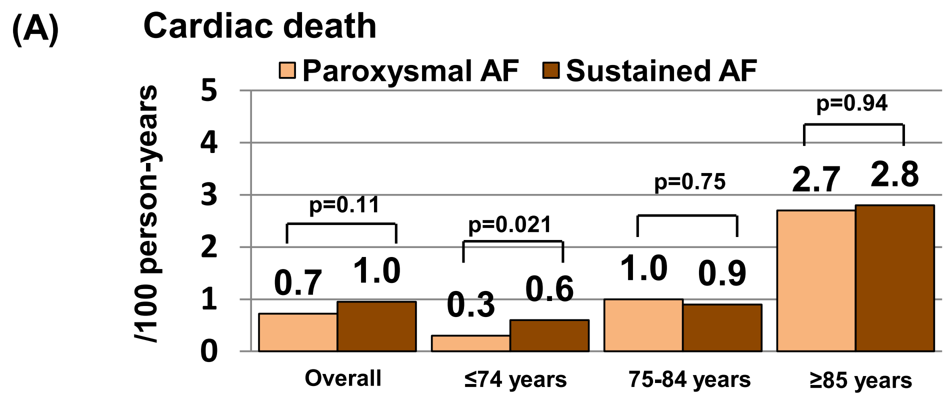
Cardiac death was mainly due to HF in the both 2 groups (Table 2), and its event rate tended to be higher in the sustained AF group than in paroxysmal AF. Figure 2 summarizes the event rate of the cardiac death and HF hospitalization in the 2 groups. The event rate of cardiac death was significantly higher in sustained AF than in paroxysmal AF, only at the age of ≤74 years (sustained AF vs paroxysmal AF, 0.6 vs 0.3 per 100 person-years; p = 0.021), but comparable at the other older age subgroups (75 to 84 and ≥85 years). HF hospitalization occurred more frequently in sustained AF than in paroxysmal AF with the higher event rate as age became older. As shown in Figure 3, the cumulative incidence of the composite of cardiac death

Table 2
Causes of death in overall patients

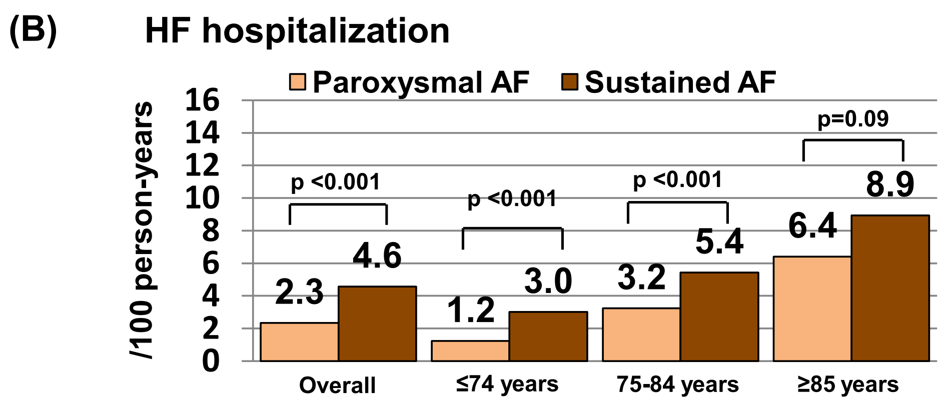
	Paroxysmal AF (n = 2,117)				Sustained AF (n = 2,187)				p value
	Number	Percentage	Event rate (/100 person-years)	95% CI (event rate)	Number	Percentage	Event rate (/100 person-years)	95% CI (event rate)	
All-cause death	358	100.0%	4.7	4.2-5.2	452	100.0%	6.0	5.4-6.6	<0.001
Cardiovascular causes	82	22.9%	1.1	0.9-1.3	120	26.5%	1.6	1.3-1.9	0.006
Cardiac	55	15.4%	0.7	0.6-0.9	72	15.9%	1.0	0.8-1.2	0.11
Heart failure	47	13.1%	0.6	0.5-0.8	67	14.8%	0.9	0.7-1.1	0.054
Acute coronary syndrome	3	0.8%	0.04	0.01-0.1	1	0.2%	0.01	0.0-0.07	0.38
Dysrhythmia	5	1.4%	0.07	0.03-0.15	4	0.9%	0.05	0.02-0.14	0.77
Vascular	27	7.5%	0.35	0.24-0.51	48	10.6%	0.6	0.5-0.8	0.014
Ischemic stroke	12	3.4%	0.16	0.09-0.27	26	5.8%	0.34	0.23-0.50	0.022
Systemic embolism	0	0.0%	0	0	1	0.2%	0.01	0.0-0.07	0.50
Hemorrhagic stroke	4	1.1%	0.05	0.02-0.13	9	2.0%	0.1	0.06-0.2	0.17
Other intracranial hemorrhage	1	0.3%	0.01	0.0-0.07	2	0.4%	0.03	0.01-0.1	0.62
Extracranial bleeding	4	1.1%	0.05	0.02-0.13	5	1.1%	0.07	0.03-0.1	0.74
Other vascular/unknown	6	1.7%	0.08	0.04-0.17	5	1.1%	0.07	0.03-0.1	0.79
Non-cardiovascular causes	206	57.5%	2.7	2.4-3.1	240	53.1%	3.2	2.8-3.6	0.086
Undetermined causes	70	19.6%	0.9	0.7-1.2	92	20.4%	1.2	1.0-1.5	0.073

CI = confidence interval.

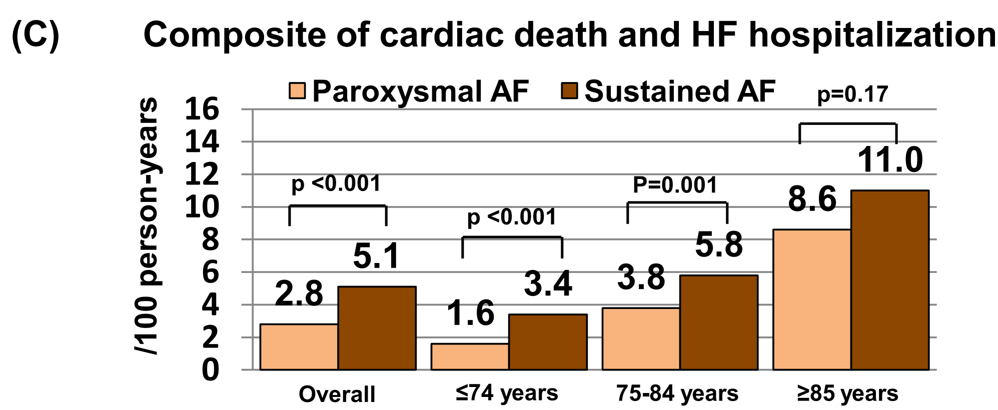
Event rates of each specific cause of death are presented per 100 person-years.



	Overall		≤74 years		75-84 years		≥85 years	
Number of event	55	72	11	22	25	26	19	24
Unadjusted HR	1.32		2.32		0.91		1.01	
95% CI	0.93-1.87		1.15-4.97		0.53-1.59		0.56-1.87	



	Overall		≤74 years		75-84 years		≥85 years	
Number of event	173	318	53	108	79	143	41	67
Unadjusted HR	1.93		2.42		1.67		1.40	
95% CI	1.61-2.33		1.75-3.39		1.28-2.21		0.95-2.08	



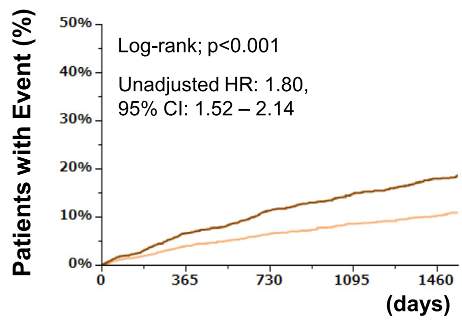
	Overall		≤74 years		75-84 years		≥85 years	
Number of event	208	357	61	123	92	152	55	82
Unadjusted HR	1.79		2.40		1.52		1.27	
95% CI	1.52-2.14		1.77-3.28		1.18-1.98		0.90-1.11	

Figure 2. Event rates of (A) cardiac death, (B) HF hospitalization, and (C) the composite of cardiac death and HF hospitalization between paroxysmal and sustained AF groups across age subgroups (≤74 years, 75 to 84 years, and ≥85 years). CI = confidence interval; HF = heart failure; HR = hazard ratio.

Paroxysmal AF — Sustained AF —

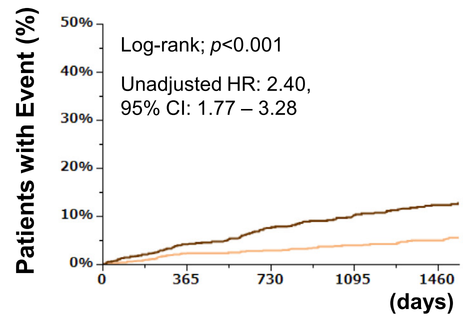
Composite of cardiac death and HF hospitalization

A Overall population



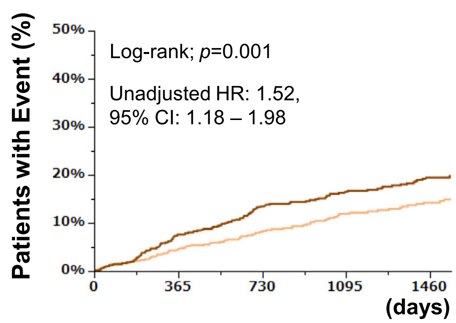
Sustained AF					
Patients at risk	2,187	1,824	1,400	1,091	835
Incidence		6.5%	11.3%	14.8%	17.9%
Paroxysmal AF					
Patients at risk	2,117	1,852	1,501	1,239	926
Incidence		2.9%	6.4%	8.5%	10.3%

B ≤74 years



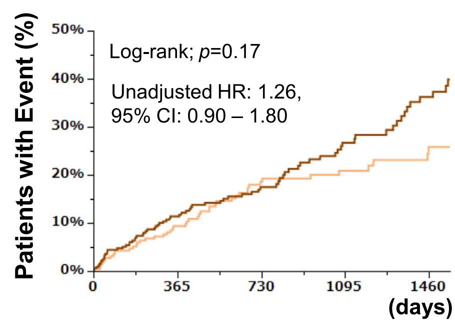
Sustained AF					
Patients at risk	1,008	884	707	574	453
Incidence		4.2%	7.6%	10.2%	12.3%
Paroxysmal AF					
Patients at risk	1,111	1,019	882	754	575
Incidence		2.1%	2.8%	3.9%	4.9%

C 75-84 years



Sustained AF					
Patients at risk	830	699	533	415	315
Incidence		7.6%	13.5%	16.5%	19.4%
Paroxysmal AF					
Patients at risk	746	636	495	390	300
Incidence		4.6%	8.2%	11.9%	14.3%

D ≥85 years



Sustained AF					
Patients at risk	349	246	163	103	59
Incidence		11.4%	17.5%	26.7%	36.2%
Paroxysmal AF					
Patients at risk	260	198	133	96	54
Incidence		9.3%	18.6%	20.9%	25.8%

Figure 3. Kaplan-Meier curves for the incidences of the composite of cardiac death and HF hospitalization between paroxysmal and sustained AF groups (A) in the overall population, (B) in patients at age of ≤74 years, (C) in those at age of 75 to 84 years, and (D) in those at age of ≥85 years.

and HF hospitalization in the overall population was significantly higher in sustained AF than in paroxysmal AF group. That of the composite end point was higher in the sustained AF group at both age of ≤74 years and 75 to 84 years. On the other hand, at the age of ≥85 years, there was no significant difference between paroxysmal and sustained AF groups.

On the multivariate Cox regression analysis (Figure 4), the incidence of the composite of cardiac death and HF hospitalization was associated with AF type only in younger AF patients (≤74 years; adjusted HR: 2.03, 95% CI: 1.44 to 2.86) but not in the other older age groups (75 to 84, and ≥85 years). Subgroup analysis on the relation of sustained versus paroxysmal AF to the composite of cardiac death

Adjusted hazard ratio of sustained AF versus paroxysmal AF

	Event number	Adjusted hazard ratio (95% CI)
Cardiac death	127	1.03 (0.70-1.53)
≤74 years	33	2.54 (1.21-5.66)
75-84 years	51	0.71 (0.38-1.35)
≥85 years	43	0.84 (0.43-1.69)
HF hospitalization	491	1.42 (1.16-1.75)
≤74 years	161	2.00 (1.39-2.92)
75-84 years	222	1.14 (0.84-1.54)
≥85 years	108	1.30 (0.84-2.06)
Composite end-point	565	1.35 (1.12-1.63)
≤74 years	184	2.03 (1.44-2.86)
75-84 years	244	1.08 (0.81-1.44)
≥85 years	137	1.17 (0.79-1.74)

composite end-point:
cardiac death and HF hospitalization

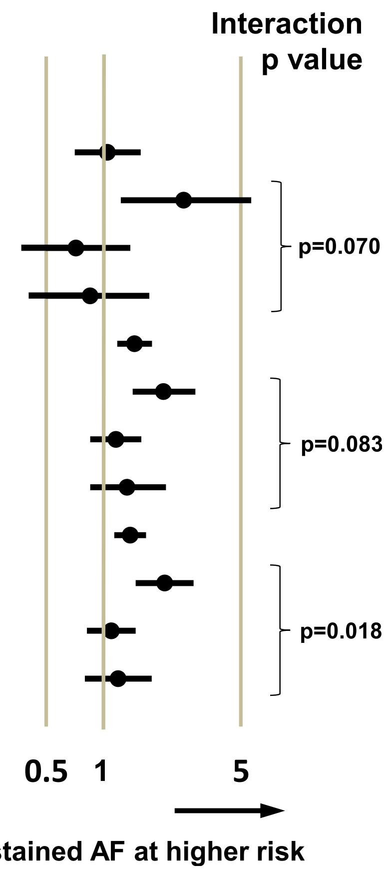


Figure 4. Adjusted HR of sustained AF versus paroxysmal AF for cardiac death, HF hospitalization, and the composite of cardiac death and HF hospitalization. Data are presented HR and 95% CI. HR was adjusted by age (not included for each age subgroup analysis), sex, body mass index as the 3 categorical variable, sustained AF (vs paroxysmal AF), pre-existing HF, hypertension, diabetes mellitus, previous stroke or TIA, peripheral artery disease, previous myocardial infarction, anemia, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, and renal dysfunction at baseline.

and HF hospitalization indicated significantly relevant interaction (p = 0.037), between patients with anemia (adjusted HR: 1.46, 95% CI: 0.88 to 2.42) and those without (adjusted HR: 3.09, 95% CI: 1.88 to 5.30) among younger AF patients (≤74 years; Figure 5). For other major subgroups, there was no significance in the interaction between the 2 groups. A selection impact analysis revealed that the HR of sustained versus paroxysmal AF among the younger group in the incidences of composite end points became lower when the age threshold for the group was over 75 years (Figure S1).

Discussion

In a Japanese community-based AF cohort, we observed a higher hazard risk of sustained AF for the incidence of the composite end point of cardiac death and HF hospitalization, compared with paroxysmal AF, that was apparent only in younger AF patients (≤74 years) but not in the other older age groups (75 to 84, and ≥85 years) on multivariate analysis. Thus, the prognostic impacts of clinical backgrounds including AF type on the composite end point varied substantially, depending on age.

Cardiac death, mainly due to HF, was the most common cause of cardiovascular death among AF patients in some recent studies.[5−7] In our community-based Japanese cohort, HF accounted for about 16% of all-cause death in each of the age subgroups (≤74, 75 to 84, and ≥85 years), which was higher than that of stroke, as we recently reported.[8] Given the heterogeneity with respect to the causes and conditions of HF, therapeutic strategies should be tailored to each individual's CV co-morbidities. Age itself is one of the important clinical factors, and clinical characteristics and prognostic indicators of mortality were different between younger and older age groups with HF.[16,17] In the present study, the prognostic impacts of the AF type (paroxysmal AF vs sustained AF) on the composite of cardiac death and HF hospitalization were different among age subgroups. This difference may be partly due to the higher prevalence of other CV and non-CV co-morbidities, in accordance with age. In fact, the present study population includes elderly AF patients (75 to 84, and ≥85 years) with

Subgroup analysis for composite of cardiac death and HF hospitalization in patients with age ≤74 years

Subgroup	No. of patients PAF	No. of patients SAF	No. of events PAF	No. of events SAF	Adjusted hazard ratio (95% CI)	Interaction p value
Overall	**1,111**	**1,008**	**61**	**123**	**2.03 (1.44-2.86)**	
Pre-existing HF						**0.80**
Yes	**135**	**290**	**25**	**73**	**2.11 (1.29-3.55)**	
No	**976**	**718**	**36**	**50**	**1.80 (1.11-2.97)**	
Anemia						**0.037**
Yes	**256**	**200**	**36**	**36**	**1.46 (0.88-2.42)**	
No	**758**	**743**	**23**	**82**	**3.09 (1.88-5.30)**	
Renal dysfunction						**0.66**
Yes	**340**	**376**	**33**	**67**	**1.94 (1.21-3.16)**	
No	**672**	**565**	**27**	**52**	**1.95 (1.18-3.31)**	
Diabetes						**0.77**
Yes	**265**	**253**	**26**	**42**	**1.81 (1.05-3.21)**	
No	**846**	**755**	**35**	**81**	**2.12 (1.37-3.37)**	
Hypertension						**0.42**
Yes	**672**	**606**	**44**	**83**	**1.88 (1.26-2.83)**	
No	**439**	**402**	**17**	**40**	**2.41 (1.26-4.84)**	
Female						**0.94**
Yes	**377**	**275**	**18**	**30**	**1.62 (0.83-3.23)**	
No	**734**	**733**	**43**	**93**	**2.14 (1.44-3.23)**	

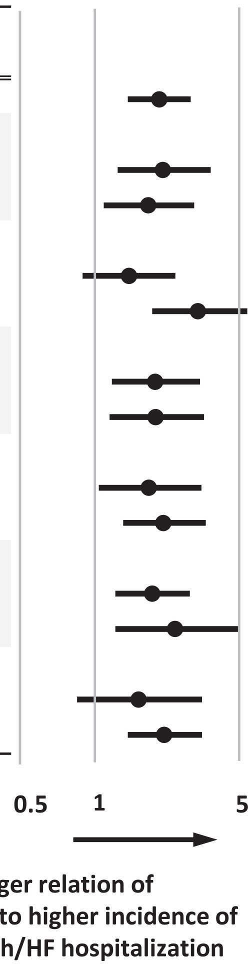


Figure 5. Adjusted HR for the composite of cardiac death and HF hospitalization in patients with age ≤74 years, according to major subgroups. Forest plots show HR with error bars indicating 95% CI. PAF = paroxysmal atrial fibrillation; SAF = sustained atrial fibrillation.

many co-morbidities who were not suitable for OAC or rhythm- and/or rate-control therapy, because of the lack of various exclusion criteria like randomized controlled trials. These clinical backgrounds as well as the AF type are also important indicators for cardiac death and HF hospitalization, which may interact with each other, along with the differential impact on outcomes, depending on age.

Recent studies, including subanalyses of randomized controlled trials[1–3] and real-world cohorts[4,18] have sought to investigate whether the AF type affects the risk of thromboembolism and all-cause mortality, although these issues are still controversial. According to the previous studies,[19–22] evaluating the predictors of incident HF, the AF type was listed as a risk factor for HF in an analysis from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)[22] and not in the others.[19–21] The present study demonstrated that sustained AF, especially in younger AF patients (≤74 years), was associated with a higher incidence of the composite of cardiac death and HF hospitalization than paroxysmal AF, even after adjustment by multivariate analysis. The differences in the predictors of subsequent HF event among the previous studies[19–22] and the present study, may be partly due to differences in clinical backgrounds, enrollment periods, and study designs. For instance, 1 report[21] included AF patients with pre-existing HF; New York Heart Association class 1; 14%, and class 2 to 4; 21% of the study population. The others[19,20,22] did not include patients with pre-existing HF and evaluated the predictors of new-onset HF. In the present study, the higher risk of sustained AF for the composite of cardiac death and HF hospitalization, compared with paroxysmal AF, may indicate the association of increased AF burden with higher cardiac event. Recently, the CASTLE-AF (Catheter Ablation vs Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trial[23] reported that catheter ablation was associated with lower rates of death from any cause and lower rates of hospital admission for heart failure along with reducing AF burden, on the basis of the data extracted from the memory of the implanted devices. Rhythm-control strategies aimed at the reduction of AF burden may be more beneficial for the prevention of adverse cardiac events in younger patients (≤74 years) with sustained AF, compared with the elderly.

The results of the present study have several limitations. First, the results were derived from a prospective observational study; therefore, it only shows the association and not causality with the limitations inherent to the design such as selection bias and unmeasured confounders, although we attempted to control confounders by adjustment using multivariate analysis. Second, the present study was conducted in an urban district in Japan. The results cannot be easily extrapolated to other rural areas or countries. Third, the currently used clinical AF classifications may poorly reflect the AF temporal persistence, as demonstrated in a recent study about patients with cardiac implantable device.[24] Our clinical classification of paroxysmal AF is likely to reflect lower AF burden compared with sustained AF, although accurate classification of AF type and evaluation of AF burden may be difficult in the routine clinical practice. Finally, the present study was based on cross-sectional analyses with clinical details at the time of enrollment, not just before the clinical adverse event. Changes of clinical backgrounds during the follow-up such as AF progression from paroxysmal to sustained type, and treatments including OAC and antiarrhythmic drug prescriptions as well as the procedure of catheter ablation and cardiac device implantation in each individual patient were also not taken into consideration.

Disclosures

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M. Akao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Other Contributions

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Supplementary materials

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1. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;34:2464–2471.
2. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP, ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;36:288–296.
3. Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E, ENGAGE AF-TIMI 48 Investigators. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 Trial (effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48). *Circ Arrhythm Electrophysiol* 2017;10.
4. Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, Iguchi M, Masunaga N, Ogawa H, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GY, Akao M. Incidence of stroke or systemic embolism in paroxysmal versus sustained atrial fibrillation: the Fushimi Atrial Fibrillation Registry. *Stroke* 2015;46:3354–3361.
5. Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2016;68:2508–2521.
6. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, Ten Cate H, Turpie AG, Verheugt FW, Kakkar AK, GARFIELD-AF Investigators. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016;37:2882–2889.
7. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, Ivanes F, Babuty D, Lip GY. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med* 2016;129:1278–1287.
8. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M. Causes of death in Japanese patients with atrial fibrillation: the Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019;5:35–42.
9. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920–2925.
10. Bai Y, Wang YL, Shantsila A, Lip GYH. The global burden of atrial fibrillation and stroke: a systematic review of the clinical epidemiology of atrial fibrillation in Asia. *Chest* 2017;152:810–820.
11. Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, Hasegawa K, Tsuji H, Furuke K, Fushimi AFRI. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. *J Cardiol* 2013;61:260–266.
12. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104–132.
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–2962.

14. Ogawa H, An Y, Ikeda S, Aono Y, Doi K, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M, Fushimi AFRI. Progression from paroxysmal to sustained atrial fibrillation is associated with increased adverse events. *Stroke* 2018;49:2301–2308.
15. Yamashita Y, Hamatani Y, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M. Clinical characteristics and outcomes in extreme elderly (age >/= 85 years) Japanese patients with atrial fibrillation: the Fushimi AF Registry. *Chest* 2016;149:401–412.
16. Stein GY, Kremer A, Shochat T, Bental T, Korenfeld R, Abramson E, Ben-Gal T, Sagie A, Fuchs S. The diversity of heart failure in a hospitalized population: the role of age. *J Card Fail* 2012;18:645–653.
17. Metra M, Cotter G, El-Khorazaty J, Davison BA, Milo O, Carubelli V, Bourge RC, Cleland JG, Jondeau G, Krum H, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Rainisio M, Kobrin I, McMurray JJ, Teerlink JR. Acute heart failure in the elderly: differences in clinical characteristics, outcomes, and prognostic factors in the VERITAS Study. *J Card Fail* 2015;21:179–188.
18. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Dan GA, Kalarus Z, Tavazzi L, Maggioni AP, Lip GY. 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Pilot Registry. *Europace* 2016;18:648–657.
19. Schnabel RB, Rienstra M, Sullivan LM, Sun JX, Moser CB, Levy D, Pencina MJ, Fontes JD, Magnani JW, McManus DD, Lubitz SA, Tadros TM, Wang TJ, Ellinor PT, Vasan RS, Benjamin EJ. Risk assessment for incident heart failure in individuals with atrial fibrillation. *Eur J Heart Fail* 2013;15:843–849.
20. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Lip GY. Predictors and prognostic implications of incident heart failure following the first diagnosis of atrial fibrillation in patients with structurally normal hearts: the Belgrade Atrial Fibrillation Study. *Eur J Heart Fail* 2013;15:415–424.
21. Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, Oikawa Y, Yajima J, Koike A, Nagashima K, Kirigaya H, Sawada H, Aizawa T, Yamashita T. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. *Am J Cardiol* 2012;110:678–682.
22. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC, ORBIT-AF Investigators and Patients. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Heart Fail* 2017;5:44–52.
23. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, Investigators C-A. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378:417–427.
24. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol* 2014;63:2840–2848.