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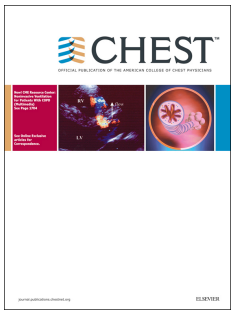

Clinical Impact of Asymptomatic Presentation Status in Patients with Paroxysmal and Sustained Atrial Fibrillation: The Fushimi AF Registry

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Abstract

Background: The clinical characteristics and outcomes of asymptomatic patients with paroxysmal or

persistent/permanent atrial fibrillation (AF) are largely unknown.

Methods: The Fushimi AF Registry is a community-based prospective survey of AF patients who visited the participating medical institutions in Fushimi-ku, Japan. We investigated the clinical characteristics and outcomes of asymptomatic versus symptomatic patients in the paroxysmal (n=1,837) and persistent/permanent (as sustained: n=1,912) AF subgroups.

Results: In the paroxysmal AF (PAF) group, asymptomatic patients were older (*asymptomatic vs. symptomatic*: 74.1 vs. 71.1 years of age; p<0.01), more often male (62.1% vs. 55.6%; p<0.01), and had a higher CHA_2DS_2-VASc score (mean 3.37±1.73 vs. 2.99±1.63; p<0.01), while the prevalence of major comorbidities and CHA_2DS_2-VASc scores were comparable in the sustained AF (SAF) group. Multivariable analysis indicated that age (≥75 years), history of stroke/SE, male sex, and chronic kidney disease were independent determinants of asymptomatic status in the PAF group, while age was non-significant in the SAF group. During the follow-up period, all-cause mortality was significantly higher (hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.31-2.29; p<0.01) in asymptomatic patients compared with symptomatic patients in the PAF group, while it was comparable in the SAF group.

Conclusions: Asymptomatic clinical status is associated with older age, males, more co-morbidities with higher stroke risk profile, and a higher incidence of all-cause death in patients with PAF, whereas these characteristics and outcomes were not seen in the SAF group.

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Introduction

Detection and diagnosis of atrial fibrillation (AF) can be challenging in patients who are asymptomatic or minimally symptomatic, regardless of whether it is paroxysmal or persistent/permanent.[1] Undiagnosed asymptomatic AF is important and may lead to a first presentation with acute ischaemic stroke or decompensated heart failure.[2]

Several studies have compared the clinical characteristics and outcomes in asymptomatic and symptomatic AF patients; however, the majority of patients in these studies had persistent or permanent AF, and were reported from Western population cohorts.[3-5] There are limited data on differences in the clinical characteristics and outcomes of community-based asymptomatic AF patients with paroxysmal and persistent/permanent AF, particularly from Asian cohorts.

The aim of this study was to investigate the clinical profile and outcomes of asymptomatic AF patients, when compared with symptomatic patients, with paroxysmal and sustained (i.e. persistent/permanent) AF from the Fushimi AF registry, a community-based prospective survey of Japanese patients with AF.[6-8]

Methods

Study Cohort

The detailed study design, patient enrollment, the definition of measurements, and subjects' baseline clinical characteristics in the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834).[6] The inclusion criterion for the registry is the documentation of AF on a 12-lead ECG or Holter monitoring at any time. There are no exclusion criteria. Patient enrollment was started in March 2011. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was

approved by the ethics committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

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Cohort Classification

The entire cohort was divided into two subgroups of AF defined as follows: (i) Paroxysmal AF (PAF), defined as self-terminating episodes lasting less than 7 days; and (ii) Sustained AF (SAF), defined as either persistent (episodes lasting longer than 7 days which can be terminated either by pharmacological therapy or electric cardioversion) or permanent (AF that is accepted by the patient (and physician), for which rhythm control interventions are not pursued) AF.[9,10] The patients were subsequently differentiated as being either asymptomatic or symptomatic at the time of enrollment based on their physicians' diagnosis and/or discretion. The symptoms of each patient were broadly described as one of the following: palpitations, orthopnea, fatigue, chest pain, and faintness; and patients were categorized into asymptomatic when the patient did not have any symptoms. The baseline characteristics and clinical outcomes of asymptomatic and symptomatic AF patients were compared in the PAF and SAF groups.

Study Endpoints

The clinical endpoints in this analysis were the incidence of stroke/SE, all-cause mortality, heart failure (HF) admission, and major bleeding during the follow-up period. These endpoints were also analyzed in the subgroups stratified by OAC use at baseline. OACs included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, and the diagnosis of ischemic or hemorrhagic stroke was

confirmed by computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organ. Major bleeding was defined as a reduction in the hemoglobin level of ≥2 g/dl, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ. HF was defined by clinical symptoms and signs, with a comprehensive examination to confirm the underlying cardiac disorder.

Statistical Analyses

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. We compared categorical variables using the chi-square test when appropriate; otherwise, we used the Fisher's exact test. The Kaplan-Meier method was used to estimate the cumulative incidence of each clinical event. We conducted a multivariable analysis using a logistic regression method to investigate the independent determinants of asymptomatic clinical status. The covariates chosen to be included in model were male sex, coronary artery disease, chronic kidney disease (CKD; persistent proteinuria or estimated glomerular filtration rate<60ml/min/1.73m^2),[11] and components of the CHA_2DS_2-VASc risk score (congestive heart failure, hypertension, age≥75 years, diabetes mellitus, history of stroke, vascular disease, age 65-74 years and female sex).[12] A multivariable Cox proportional hazard model was used to calculate the hazard ratios (HRs) of asymptomatic status for major clinical events in the PAF patients. Covariates chosen to be included in the model were age, body weight, history of stroke/SE, history of heart failure, hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, CKD, and history of major bleeding.

Data were analyzed with the use of the online software, 'EZR' (Easy R 32-bit version; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html), for Windows.[13] A two-sided P-value<0.05

was considered statistically significant. Confidence intervals (CI) are reported as 95%.

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Results

A total of 4,484 patients were enrolled by the end of December 2015. Of the 4,185 patients who were enrolled 1 year prior (by the end of December 2014), follow-up data (collected every year) were available for 3,749 patients (follow-up rate: 89.6%). Of these 3,749 patients, 1,971 patients (52.6%) were asymptomatic, and the remaining 1,778 (47.4%) patients were symptomatic; 1,837 patients (49%) had PAF and 1,912 patients (51%) had SAF. Furthermore, 689 patients (37.5%) and 1,282 patients (67.1%) were asymptomatic in the PAF and SAF group, respectively. Median follow-up was 1,099 days (IQR 479–1719 days).

Baseline Clinical Characteristics

Mean (±SD) age and CHA_2DS_2-VASc score in the entire cohort were 73.6 (±11) years, and 3.37 (±1.7), respectively. Asymptomatic patients were older, and had a higher mean CHA_2DS_2-VASc score than symptomatic patients in the entire cohort (asymptomatic vs. symptomatic: 74.7 (±10.6) vs. 72.4 (±11.3); $P<0.01$, and 3.49 (±1.72) vs. 3.23 (±1.68); $P<0.01$, respectively).

Baseline clinical characteristics of asymptomatic and symptomatic patients in both the PAF and SAF groups are summarized in Table 1. In the PAF group, asymptomatic patients were more often male, older, and were more likely to have a history of stroke/SE, CKD, and major bleeding. Both the mean $CHADS_2$ and CHA_2DS_2-VASc scores were higher in asymptomatic patients. There was less use of class I antiarrhythmic drugs (AAD), and β-blockers in the asymptomatic patients compared with symptomatic ones, whereas the OAC use was similar. In the SAF group, asymptomatic patients were often male and were more likely to

have a history of stroke/SE, but the mean $CHADS_2$ and CHA_2DS_2-VASc scores were similar. There was a lower rate of class I antiarrhythmic drug (AAD), β-blocker, and diuretics use in asymptomatic patients. The use of OACs was also lower in asymptomatic patients than in symptomatic patients. A lower proportion of asymptomatic patients underwent invasive catheter ablation compared with symptomatic patients in both PAF and SAF groups.

On multivariable logistic regression analysis, male sex, age (≥75 years), CKD, history of stroke/SE, and major bleeding were significantly associated with asymptomatic status in the PAF group, after adjusting for several covariates including the components of the CHA_2DS_2-VASc score (Table 2). In the SAF group, the same covariates as in the PAF group, with the exception of age, were also significantly associated with asymptomatic status.

Clinical Outcomes

Major clinical events in the PAF or SAF group and in the entire cohort during the follow-up period are shown in Table 3. Kaplan-Meier curves for the incidences of stroke/SE, all-cause mortality, HF admission, and major bleeding are shown in Figure 1 (PAF group) and Figure 2 (SAF group).

In the PAF group, all-cause mortality was significantly higher in asymptomatic patients compared with symptomatic patients (asymptomatic versus symptomatic: 7.25 versus 3.70 per 100 person-years; P<0.01, Table 3). The mortality between asymptomatic PAF group and the entire SAF group was non-significantly different (7.25 versus 6.67 per 100 person-years; P=0.11). All the other outcomes (stroke/SE, HF admission, and major bleeding) were non-significantly different between asymptomatic and symptomatic patients in PAF.

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On multivariable analysis, asymptomatic status was significantly associated with the higher mortality in PAF patients after adjusting for potential confounders (HR, 1.71; 95% CI, 1.31-2.29; P<0.01) (Table 4). The higher risk of mortality persisted even when the PAF patients were stratified by OAC status (With OAC: HR, 1.74; 95% CI, 1.12-2.71, Without OAC: HR, 1.68; 95% CI, 1.20-2.34) (Table 4). All clinical outcomes were non-significantly different between asymptomatic and symptomatic patients in the SAF group (Table 3).

Finally, we explored the risk factors of all-cause death in the PAF patients, using multivariable logistic regression analysis. As shown in the Table 5, after adjusting for confounders, asymptomatic status was an independent risk factor of the incidence of all-cause death during the follow-up period in the PAF group (HR: 1.73, 95% CI: 1.29-2.33; P<0.01).

Discussion

In this large community-based Asian cohort from Japan comparing characteristics and outcomes between paroxysmal and sustained AF patients in relation to symptomatic status, our principal findings are as follows: (i) asymptomatic patients have more comorbidities with higher $CHADS_2$ and CHA_2DS_2-VASc scores, a higher incidence of all-cause death compared with symptomatic patients in the PAF group, whereas these characteristics and outcomes were not seen in the SAF group; (ii) independent determinants of asymptomatic presentation were male sex, age, CKD, and prior history of stroke/SE or major bleeding in the PAF group, but not age in the SAF group; and (iii) all-cause mortality was higher in asymptomatic patients compared to symptomatic patients in the PAF group, with asymptomatic clinical status being an independent risk factor for all-cause mortality.

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Clinical profile of asymptomatic patients

Asymptomatic AF is common in daily "real-world" clinical practice[14-16]. However, the relationship between patient characteristics and symptom presentation has not been consistent across studies and therefore remains controversial. Additionally, these relationships have not been studied in community-based PAF and SAF groups, nor in Asian AF cohorts.

In the present study, we show distinct clinical characteristics of asymptomatic and symptomatic patients in the PAF group, rather than those in the SAF group. There were more comorbidities with higher $CHADS_2$ and CHA_2DS_2-VASc scores in asymptomatic patients than in symptomatic in the PAF group, while these were similar in the SAF group; however, asymptomatic PAF and SAF patients have similar risks of thromboembolism. The proportions of invasive and medical treatments were similar or less frequent in asymptomatic patients compared with symptomatic patients in both the PAF and SAF groups, indicating that the symptomatic status is likely to affect the physicians' decision on treatment strategy in both PAF and SAF patients.

Male sex, CKD, and history of stroke/SE or major bleeding were significantly associated with asymptomatic status both in the PAF and SAF group. The higher prevalence of asymptomatic status in male was consistent with previous reports.[17] Nonetheless, we recognize that CKD and previous stroke/SE or major bleeding may be related to physical disability and/or inactivity, which could make patients asymptomatic.

Clinical outcomes of asymptomatic patients in the paroxysmal and sustained AF groups

In the present study, all-cause mortality was higher in asymptomatic than symptomatic patients, but only in the PAF group. In a study by Boriani et al.,[3,15] asymptomatic patients were associated with more

comorbidities, higher CHA_2DS_2-VASc score, and had higher mortality, compared with symptomatic patients. They therefore concluded that asymptomatic AF is not benign but is associated with a higher mortality risk, inconsistent with prior randomized clinical trials.[5,18] Our present data also demonstrate worse clinical outcomes of asymptomatic patients compared with those of symptomatic patients in the PAF group, but not in the SAF group. One possible reason of these distinct outcomes between the PAF and SAF subgroups may be due to the difficulty of AF detection in patients with PAF compared with SAF. SAF can be easily detected with routine ECG even in the absence of symptoms, but PAF would be less easily detected, especially if asymptomatic. Hence, optimal AF management would be delayed or inappropriate, including OAC treatment. Indeed, asymptomatic patients were older, with more comorbidities and higher CHA_2DS_2-VASc score compared with symptomatic patients in the PAF group, perhaps because those patients were more likely to be undetected. In contrast, differences between asymptomatic and symptomatic patients were not observed in SAF group, which suggests similarity of AF detection irrespective of patients' symptoms.

Recent studies have reported that the patients with PAF had a lower rate of stroke/SE or mortality than those with SAF.[19,20] However, our present findings suggest that these outcomes were not applicable in terms of the asymptomatic clinical status. Our present study highlights the worse outcomes of asymptomatic PAF patients, that are comparable to those in patients with SAF, thus emphasizing the importance of early AF detection and holistic management in daily cardiology practice.

Limitations

Several limitations should be acknowledged in interpreting the results of the present study. First, the results

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are derived from an observational study, and describes associative, not causative evidence. The present data were derived from an urban district in Japan, and therefore the results cannot be easily extrapolated to other rural areas, countries, or population-based registries. Second, OAC data were collected only at the time of study entry, so we could not examine the relationship between changes in OACs and clinical events. Additionally, the type of antithrombotic drugs and doses were selected at the discretion of the attending physician. Third, we did not investigate the time in therapeutic range for patients receiving warfarin during follow-up or the adherence to OAC therapies. Therefore, it is difficult to determine the influence of the quality of warfarin control and the adherence of OAC therapies on outcomes. Fourth, we were unable to assess AF burden, which might have affected the incidence of stroke/SE in patients with PAF. Fifth, the diagnosis of the type of AF, the determination of symptomatic/asymptomatic status and the classification of symptoms were physician-dependent at the time of enrollment, which may affect the clinical profiles and outcomes. Moreover, many asymptomatic patients (at enrollment) might have been previously symptomatic, but we did not have information on prior symptom status. Indeed, Boriani et al. reported the significant difference in the patient characteristics between fully asymptomatic patients and asymptomatic patients with previous symptoms.[3] Sixth, there may be some selection bias for asymptomatic patients: the higher risk profiles might be more related to age rather than symptom status, as being older usually represents a longer prior AF duration which may potentially leads to an asymptomatic status. Seventh, other minor symptoms which were not categorized into any of the five pre-defined symptom types may be overlooked. We unfortunately have no data regarding the exercise capacity of asymptomatic patients, which may have a major impact on overall outcome. Finally, we cannot rule out the possibility of unmeasured or residual confounding especially with age and co-morbidities even after the multivariate analysis.

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Despite these limitations, our study highlights the differences in the clinical profile and outcomes between asymptomatic and symptomatic patients in both the PAF and SAF cohorts. The present data also demonstrated that asymptomatic PAF patients may not receive adequate treatment, thus better identification and management of such patients with PAF would be needed.

Conclusions

In this community-based, large prospective cohort of Japanese patients with AF, asymptomatic clinical status is associated with older age, males, more co-morbidities with higher stroke risk profile, and a higher incidence of all-cause death in patients with PAF, whereas these characteristics and outcomes were not seen in the SAF group.

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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.

Author contributions: ME analyzed the data and wrote the paper. GYHL helped data analysis and interpretation. YC, YA, HW, KH, HO, and M. Abe are executive members of the organizing committee of the Fushimi AF Registry. M. Akao is a principal investigator of the Fushimi AF Registry, and the corresponding author of this paper.

Role of the sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We sincerely appreciate the efforts of the clinical research coordinators (T. Shinagawa, M. Mitamura, M. Fukahori, M. Kimura, M. Fukuyama, and C. Kamata).

Disclosures

Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare and Daiichi-Sankyo. Dr. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Figure Legends

Figure 1.

Kaplan-Meier curves for the incidences of stroke/systemic embolism (SE) (**A**), All-cause death (**B**), heart failure (HF) admission (**C**), and major bleeding (D) between asymptomatic and symptomatic patients with paroxysmal atrial fibrillation. HR indicates hazard ratio; CI, confidence interval.

Figure 2.

Kaplan-Meier curves for the incidences of stroke/systemic embolism (SE) (**A**), All-cause death (**B**), heart failure (HF) admission (**C**), and major bleeding (**D**) between asymptomatic and symptomatic patients with sustained atrial fibrillation. Abbreviations as in Figure 1.

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Tables

Table 1. Baseline clinical characteristics, co-morbidities, medical, and invasive treatment

	PAF (1,837)			SAF (1,912)		
	Asymptomatic (689)	Symptomatic (1,148)	P value	Asymptomatic (1,282)	Symptomatic (630)	P value
Baseline characteristics						
Men	428 (62.1%)	638 (55.6%)	<0.01	813 (63.4%)	344 (54.6%)	<0.01
Age –yr, mean±SD	74.1±11.5	71.1±11.7	<0.01	75±10	74.7±10.1	0.497
BMI, mean±SD	22.9±4.1	22.9±3.7	0.692	23±3.8	23.4±4.5	0.099
Basic heart rate, bpm	77.7±15.9	75.3±15.9	<0.01	79.1±15.1	80.8±17.1	0.037
LVEF<40%	24/549 (4.4%)	35/919 (3.8%)	0.586	58/1026 (5.7%)	41/456 (9%)	0.024
LAD (mm), mean±SD	40.1±6.9	40.6±7.1	0.191	47±8.1	47.5±8	0.261
Symptom type						
palpitation	-	921 (80.2%)		-	303 (48.1%)	
orthopnea	-	204 (17.8%)		-	300 (47.6%)	
fatigue	-	129 (11.2%)		-	174 (27.6%)	
chest pain	-	75 (6.5%)		-	32 (5.1%)	
faintness	-	105 (9.1%)		-	65 (10.3%)	
Co-morbidities						
$CHADS_2$, mean±SD	2.02±1.36	1.68±1.2	<0.01	2.22±1.38	2.25±1.33	0.72
CHA_2DS_2-VASc, mean±SD	3.37±1.73	2.99±1.63	<0.01	3.55±1.71	3.67±1.68	0.14
History of stroke/SE	158 (22.9%)	138 (12%)	<0.01	344 (26.8%)	129 (20.5%)	<0.01
Heart failure	133 (19.3%)	187 (16.3%)	0.112	387 (30.2%)	301 (47.8%)	<0.01
Hypertension	424 (61.5%)	729 (63.5%)	0.425	792 (61.8%)	384 (61%)	0.425
Diabetes mellitus	173 (25.1%)	243 (21.2%)	0.057	311 (24.3%)	138 (21.1%)	0.134
Coronary artery disease	119 (17.3%)	188 (16.4%)	0.651	136 (10.6%)	116 (18.4%)	<0.01
Chronic kidney disease	254 (36.9%)	341 (29.7%)	<0.01	492 (38.4%)	236 (37.5%)	0.726

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History of major bleeding	41 (6%)	25 (2.2%)	<0.01	64 (5%)	17 (2.7%)	0.021
Peripheral artery disease	38 (5.5%)	41 (3.6%)	0.057	57 (4.4%)	17 (2.7%)	0.076
Medical treatment						
OAC at baseline	273 (40%)	472 (41.3%)	0.623	806 (63.2%)	447 (71.1%)	<0.01
Antiplatelet drugs	204 (29.9%)	321 (28.1%)	0.602	358 (28.1%)	173 (27.5%)	0.828
Class I AAD	145 (21.3%)	397 (34.7%)	<0.01	47 (3.7%)	92 (14.6%)	<0.01
Class III AAD	7 (1%)	8 (0.7%)	0.593	3 (0.2%)	3 (0.5%)	0.403
Bepridil	18 (2.6%)	38 (3.3%)	0.484	12 (0.9%)	8 (1.3%)	0.34
β-blockers	153 (22.4%)	334 (29.2%)	<0.01	340 (26.5%)	245 (38.9%)	<0.01
Calcium antagonists	221 (32.4%)	376 (32.9%)	0.837	380 (29.6%)	179 (28.4%)	0.426
Digitalis	37 (5.4%)	66 (5.8%)	0.834	251 (19.6%)	107 (17%)	0.202
Diuretics	156 (22.9%)	217 (19%)	0.048	416 (32.6%)	261 (41.5%)	<0.01
Invasive treatment						
Catheter ablation	28 (4.1%)	133 (11.6%)	<0.01	21 (1.6%)	50 (7.9%)	<0.01

Categorical data are presented as number (%). Continuous data are presented as mean ± standard deviation (SD). PAF: paroxysmal atrial fibrillation, SAF: sustained atrial fibrillation, BMI: body mass index, LVEF: left ventricular ejection fraction, LAD: left atrial diameter, SE: systemic embolism, OAC: oral anticoagulants, AAD: antiarrhythmic drug.

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Table 2. Indicators of the asymptomatic clinical status – Multivariable Analysis

	PAF			SAF		
Variable	OR	95% CI	P value	OR	95% CI	P value
Heart failure	1.10	0.85-1.44	0.47	0.48	0.39-0.59	<0.01
Hypertension	0.87	0.71-1.07	0.18	1.03	0.84-1.26	0.81
Age (≥75 years)	1.31	1.07-1.60	<0.01	1.04	0.85-1.28	0.70
Diabetes mellitus	1.18	0.94-1.50	0.16	1.22	0.96-1.55	0.11
History of stroke/SE	1.90	1.46-2.46	<0.01	1.35	1.06-1.72	0.016
History of major bleeding	2.09	1.24-3.54	<0.01	1.93	1.09-3.41	0.024
Male sex	1.36	1.11-1.66	<0.01	1.39	1.13-1.70	<0.01
Coronary artery disease	0.90	0.69-1.18	0.46	0.52	0.39-0.69	<0.01
Chronic kidney disease	1.26	1.02-1.57	0.035	1.35	1.09-1.68	<0.01

Data are presented as OR (odds ratio) and 95% CI (confidence interval).

PAF: paroxysmal atrial fibrillation, SAF: sustained atrial fibrillation, SE: systemic embolism.

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Table 3. Incidence of clinical events during follow-up (/100 person-years)

	PAF		SAF	
Outcomes	Incidence rate	P value	Incidence rate	P value
Stroke/SE	1.79		2.59	
Asymptomatic	2.06	0.069	2.82	0.087
Symptomatic	1.63		2.13	
All-cause death	5.03		6.67	
Asymptomatic	7.25	<0.01	7.04	0.076
Symptomatic	3.70		5.92	
HF admission	2.33		4.35	
Asymptomatic	2.27	0.65	3.96	0.08
Symptomatic	2.37		5.15	
Major bleeding	1.66		1.87	
Asymptomatic	1.89	0.087	1.77	0.59
Symptomatic	1.53		2.07	

Data are presented as incidence rates (per 100 person-years). P value for comparison between asymptomatic versus symptomatic using a log-rank test.

PAF: paroxysmal atrial fibrillation, SAF: sustained atrial fibrillation, SE: systemic embolism, HF: heart failure.

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Table 4. Relative risk of asymptomatic status for major clinical events in the PAF patients - Multivariable Analysis

	Entire Cohort			With OAC			Without OAC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Stroke/SE	1.28	0.82-2.01	0.28	1.05	0.52-2.11	0.90	1.46	0.79-2.71	0.23
All-cause death	1.71	1.31-2.29	<0.01	1.74	1.12-2.71	0.013	1.68	1.20-2.34	<0.01
HF admission	0.96	0.65-1.44	0.86	1.19	0.71-2.00	0.78	0.78	0.42-1.46	0.44
Major bleeding	1.18	0.74-1.90	0.48	1.57	0.77-3.20	0.21	0.93	0.48-1.79	0.83

Data are presented as HR (hazard ratio) and 95% CI (confidence interval).

HR was adjusted by age, body weight, history of stroke/SE, history of heart failure, hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, chronic kidney disease, and history of major bleeding.

PAF: paroxysmal atrial fibrillation, SE: systemic embolism, HF: heart failure, OAC: oral anticoagulants.

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Table 5. Risk factors of all-cause death in the PAF patients – Multivariable Analysis

Variable	OR	95% CI	P value
Asymptomatic status	1.73	1.29-2.33	<0.01
Heart failure	2.77	1.99-3.86	<0.01
Hypertension	0.80	0.59-1.08	0.15
Age (≥75 years)	2.56	1.86-3.53	<0.01
Diabetes mellitus	1.42	1.02-1.97	0.039
History of stroke/SE	1.95	1.36-2.80	<0.01
Male sex	1.24	0.92-1.68	0.16
Coronary artery disease	1.17	0.82-1.68	0.38
Chronic kidney disease	2.10	1.54-2.85	<0.01
History of major bleeding	2.09	1.15-3.81	0.015
OAC use	0.59	0.43-0.80	<0.01

Data are presented as OR (odds ratio) and 95% CI (confidence interval).

PAF: paroxysmal atrial fibrillation, SE: systemic embolism, OAC: oral anticoagulants.

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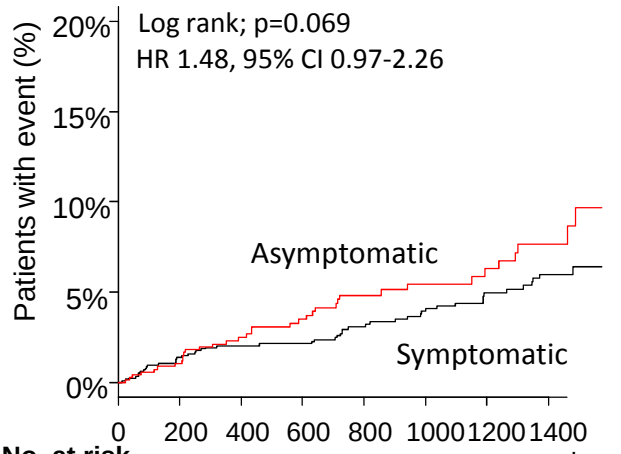
Figure 1

PAF

A

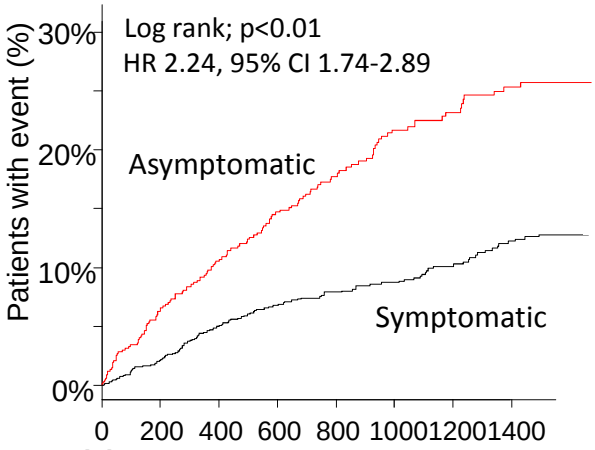
Stroke/SE



No. at risk								
Symptomatic	1148	1108	942	879	683	662	474	452
Asymptomatic	689	641	503	446	321	296	215	205

B

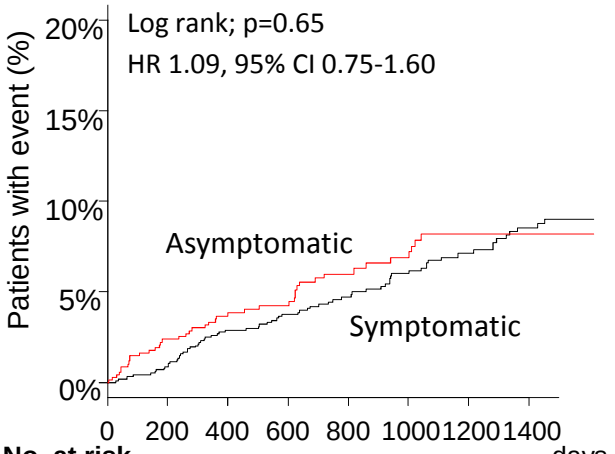
All-cause death



No. at risk								
Symptomatic	1148	1120	953	891	695	678	490	469
Asymptomatic	689	645	512	457	328	304	219	212

C

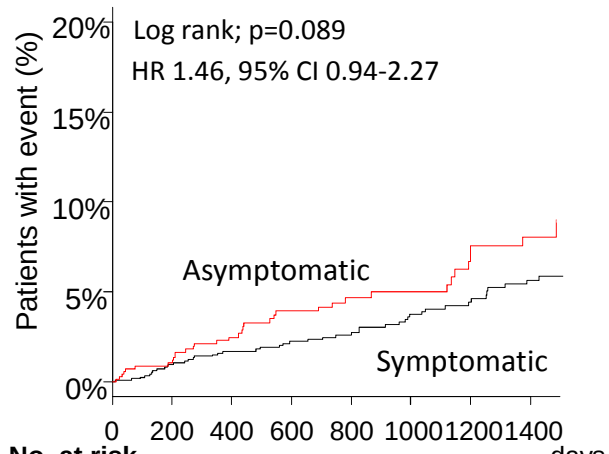
HF admission



No. at risk								
Symptomatic	1148	1113	930	864	669	644	463	440
Asymptomatic	689	632	502	447	319	295	211	205

D

Major bleeding



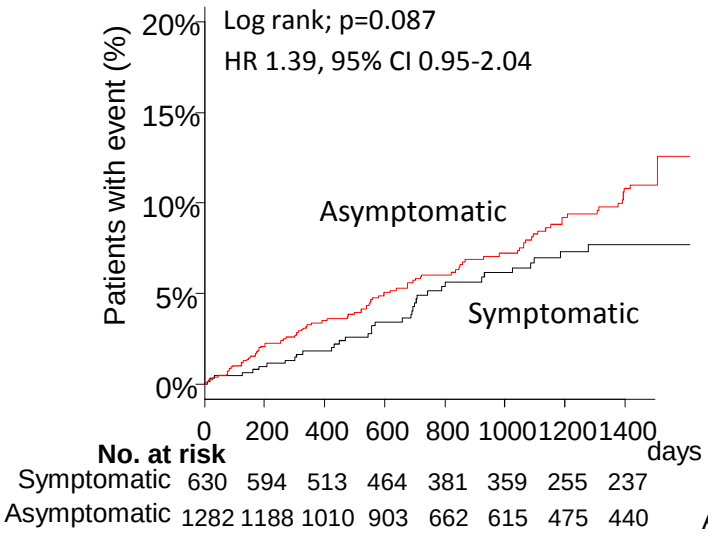
No. at risk								
Symptomatic	1148	1110	941	877	683	660	476	450
Asymptomatic	689	640	500	442	315	293	210	203

Figure 2

SAF

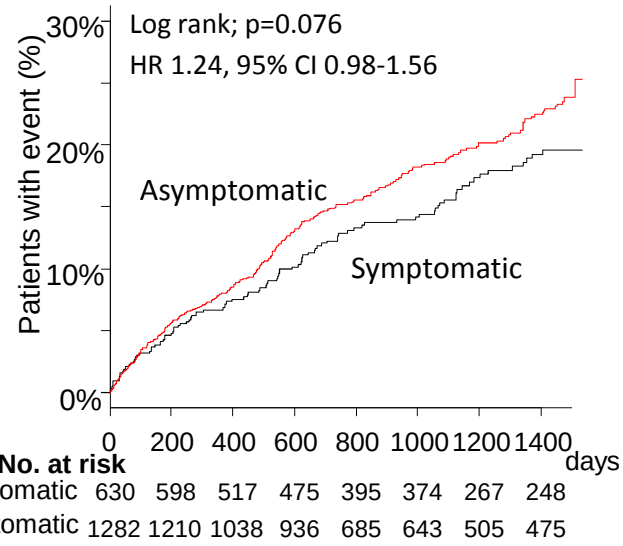
A

Stroke/SE



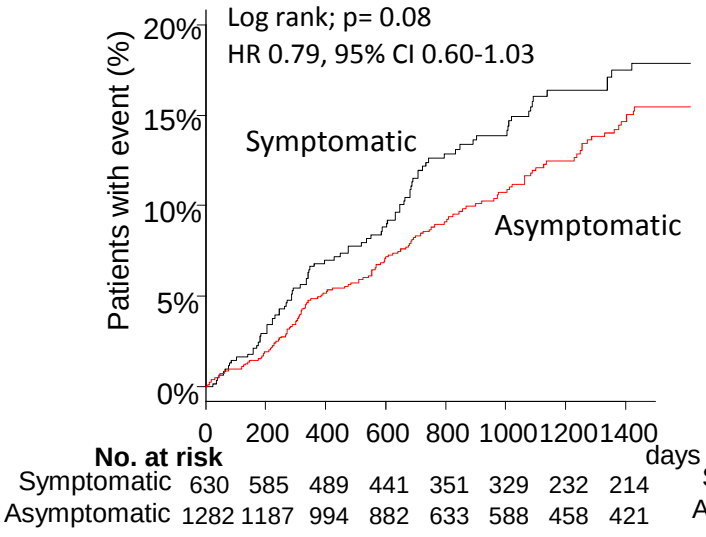
B

All-cause death



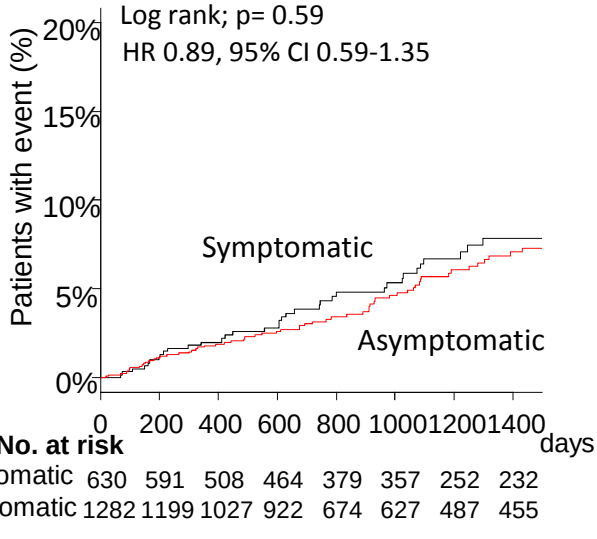
C

HF admission



D

Major bleeding



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e-Appendix 1.

Working Group Members

The following is a list of the institutions participating in the registry.

Chief investigator: Akao M (National Hospital Organization Kyoto Medical Center).

Vice-chief investigator: Chun YH (Ijinkai Takeda General Hospital).

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Coordinator: Ogawa T (Ogawa Medical Office), Tasato H (Tasato Clinic), Taniguchi Y (Taniguchi Clinic), Nishikawa M (Nishikawa Clinic), Furukawa K (Furukawa Medical Clinic), Kawai C, Hashimoto T, Kanda M (Ijinkai Takeda General Hospital), Tsukahara T, Fukuda S, Nakamura M, Ohtani R, Ito T, Hasegawa K (National Hospital Organization Kyoto Medical Center).

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(Kayawake S, Kinoshita Y); Furuke Clinic (Furuke K); Kanehisa Clinic (Asano N); Tahara Clinic (Tahara K); Matsumoto Medical Office (Matsumoto K); Kuroda Clinic (Kuroda O); Ochiai Clinic (Ochiai K, Ochiai J); Fujii Clinic (Fujii M); Kurihara Clinic (Kurihara M); Kuzuyama Clinic (Ito A); Kenkokai Fushimi Clinic (Totsuzaki S); Nakayama Orthopedic Clinic (Nakayama H); Department of Cardiovascular Medicine, Ijinkai Takeda General Hospital (Kawai C, Hashimoto T, Kakio T, Watanabe C, Takeda S, Sasaki Y, Shirasawa K, Beppu K, Inoue T, Shirasaka A, Doi T); Tatsumi Clinic (Ueda T); Oishi Clinic (Oishi M); Koizumi Clinic (Kasahara A); Kishida Clinic (Kishida Su, Kishida Sa); Shibata Clinic (Shibata M); Shimizu Clinic (Shimizu J); Shirasu Clinic (Shirasu M); Fujinokai Clinic (Tateishi S); Tsukuda Clinic (Tsukuda N); Shinseikai Tsuji Clinic (Tsuji K); Nishi Clinic (Nishi T); Nishimura Clinic (Nishimura S); Haba Clinic (Haba T); Higashimae Clinic (Higashimae R); Fujimori Clinic (Fujimori C); Hotta Clinic (Hotta T); Matsui Clinic (Matsui H, Matsui H); Shadan Matsumoto Clinic (Matsumoto H); Maruo Clinic (Maruo N); Misu Clinic (Mikami M); Mekata Clinic (Mekata H); Mori Pediatric Clinic (Mori H); Wakabayashi Clinic (Wakabayashi M); Nakatsugawa Clinic (Sasaki Z); Shiseikai Nishimura Clinic (Nishimura S); Yuge Eye Clinic (Yuge K); Gokita Hospital (Haruta M); Soseikai Clinic (Tsuda E); Toujinkai Hospital (Nishimura M); Kouno Clinic (Kouno T, Kouno Y); Matsumura Clinic (Matsumura S); Fujita Clinic (Fujita A); Takayasu Clinic (Takayasu F, Takayasu S), Yano Clinic (Yano Y), Niki Clinic (Niki S), Hasegawa Meiando Clinic (Hasegawa S), Watanabe Medical Clinic (Watanabe T).

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