Journal of the American Heart Association

ORIGINAL RESEARCH

Fine Fibrillatory Wave as a Risk Factor for Heart Failure Events in Patients With Atrial Fibrillation: The Fushimi Atrial Fibrillation (AF) Registry

Tetsuma Kawaji, MD, PhD; Hisashi Ogawa, MD; Yasuhiro Hamatani, MD, PhD; Masashi Kato, MD, PhD; Takafumi Yokomatsu, MD; Shinji Miki, MD, PhD; Mitsuru Abe, MD, PhD; Masaharu Akao, MD, PhD; on behalf of the Fushimi AF Registry investigators*

BACKGROUND: The clinical significance of fibrillatory wave on electrocardiography during atrial fibrillation (AF) is poorly understood. The aim of the current study was to explore the association of fine fibrillatory wave with heart failure (HF) in AF.

METHODS AND RESULTS: The current study enrolled 2442 patients with AF whose baseline ECG during AF rhythm was available from a community-based prospective survey, the Fushimi AF Registry. The impact of fine fibrillatory wave, defined as the amplitude of fibrillatory waves <0.1 mV, on the primary composite HF end point (a composite of hospitalization attributable to HF or cardiac death) was examined. Fine fibrillatory wave was observed in 589 patients (24.1%). Patients with fine fibrillatory wave were older, and had a higher prevalence of sustained AF, preexisting HF, and larger left atrial diameter than those with coarse fibrillatory wave. During the median follow-up duration of 5.9 years, the cumulative incidence of the primary composite HF end point was significantly higher in patients with fine fibrillatory wave than in those with coarse fibrillatory wave (5.3% versus 3.6% per patient-year, log-rank $P<0.001$). The higher risk associated with fine fibrillatory wave was consistent even for individual components of the primary composite HF end point. On multivariable analysis, fine fibrillatory wave became an independent predictor for the primary composite HF end point (hazard ratio, 1.31; 95% CI, 1.07–1.61; $P=0.01$).

CONCLUSIONS: Compared with coarse fibrillatory wave, fine fibrillatory wave was more prevalent in patients with a larger left atrial diameter or those with sustained AF and was independently associated with a higher risk of HF events.

REGISTRATION: URL: https://www.umin.ac.jp/ctr/; Unique identifier: UMIN000005834.

Key Words: atrial fibrillation ■ ECG ■ fibrillatory wave ■ heart failure

Atrial fibrillation (AF) is a common arrhythmia and is associated with poor prognosis in daily clinical practice. As we previously demonstrated that an inverted T wave during AF rhythm is associated with higher subsequent cardiac risk in patients with AF,[1] classical ECG findings during AF rhythm may include useful signs to predict subsequent cardiac risk. Fibrillatory wave is one of the ECG criteria for diagnosing AF in addition to an irregular ventricular response and reflects frequent electrical excitation in the atrium. Fine fibrillatory wave, a low-amplitude fibrillatory wave, is associated with degenerated atrial function such as large atrial size and low left atrial appendage flow.[2–4] Furthermore, several studies evaluated the association

Correspondence to: Masaharu Akao, MD, PhD, FESC, FJCS, Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto University, 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555 Japan. E-mail: akao@kuhp.kyoto-u.ac.jp

*A complete list of the Fushimi AF Registry investigators can be found in the Supplemental Material.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024341

For Sources of Funding and Disclosures, see page 7.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Fine fibrillatory wave during atrial fibrillation rhythm was associated with a higher risk for a composite of hospitalization because of heart failure or cardiac death in a community-based prospective survey.

What Are the Clinical Implications?

- Fine fibrillatory wave during atrial fibrillation rhythm may be helpful to clinicians as a simple and quick sign to evaluate heart failure risk in patients with atrial fibrillation.

between the amplitude of fibrillatory wave and thromboembolic events, which are devastating complications of AF.[4–6] However, to our knowledge, few studies have addressed the association between the amplitude of fibrillatory wave and heart failure (HF), which is another major complication of AF. Therefore, we investigated the association of fine fibrillatory wave with clinical outcomes associated with HF in patients with AF using data from the Fushimi AF Registry, a community-based survey of patients with AF in Japan.[7]

METHODS

Data Source and Study Population

We declare that all supporting data are available within the article and its online supplemental files. The detailed study design, patient enrollment, definitions of measurements, and baseline clinical characteristics of patients in the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834).[7] The inclusion criterion for the registry is the documentation of AF on a 12-lead ECG or Holter monitoring of AF at any time. There were no exclusion criteria. We started to enroll patients from March 2011 and a total of 81 institutions participated from the Fushimi district in Kyoto, Japan. Collection of follow-up information was mainly conducted through a review of 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 conformed to the 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. Since the current research is belonging to the observational study not using human biological specimens, written informed consent was not obtained from each patient according to the ethical guidelines for epidemiological research issued by Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan. However, we have published all relevant details on this study to be performed and provide each patient an opportunity to refuse inclusion in this research by posting the details at every participating clinic and at the homepages of our institutions. We also held the public meeting to the citizens in the Fushimi-ku to demonstrate outlines of the current study.

The 12-lead ECG data during documented AF rhythm were obtained from the participating institutions at enrollment. However, submission of ECG data was not required for enrollment and was optional. Among the entire cohort of 4472 patients with AF in the Fushimi AF Registry enrolled by the end of July 2019, we excluded 1579 whose ECG data were not provided from the participating institutions and 271 whose provided ECG data were only during atrial flutter or atrial tachycardia. In total, we analyzed 2442 patients whose baseline 12-lead ECG during AF rhythm at the time of enrollment was available in the current study.

Definitions and Outcome Measures

Sustained (persistent or permanent) AF was defined as AF lasting longer than 7 days. The amplitude of the fibrillatory wave was manually measured from the peak to the trough in each lead and was diagnosed by an experienced cardiologist. Fine fibrillatory wave was defined as the amplitude of fibrillatory waves <0.1 mV in all leads, and fibrillatory wave >0.1 mV in at least 1 lead was regarded as coarse fibrillatory wave.[3,5,6,8] Typical ECG tracings of fine fibrillatory wave and coarse fibrillatory wave are shown in Figure 1.

Preexisting HF was defined as the presence of 1 of the following at enrollment: history of hospitalization for HF before enrollment, presence of HF symptom (New York Heart Association functional class ≥2) in association with heart disease or reduced left ventricular ejection fraction <40%.[7] Preexisting HF with and without left ventricular ejection fraction (LVEF) <40% on transthoracic echocardiography were regarded as HF with reduced LVEF and preserved LVEF, respectively. Thromboembolic events included ischemic stroke and systemic embolism.

The primary HF end point was a composite of hospitalization because of HF or cardiac death. Death was regarded as cardiac in origin only when obvious cardiac causes were identified. The secondary end point was hospitalization because of HF, all-cause death, non-cardiac death, and cardiac death.

Statistical Analysis

Categorical variables are presented as the number and percentage and were compared using the Chi-square test or Fisher exact test. Continuous variables are

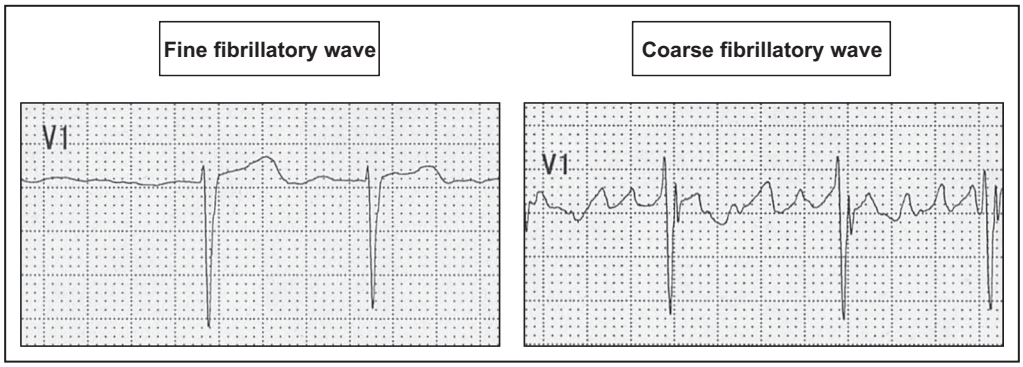


Figure 1. Definition of fine and coarse fibrillatory wave.

presented as the mean with SD or median with interquartile range and were compared using the Student *t*-test or Wilcoxon rank sum test based on their distributions. The cumulative incidence was estimated by the Kaplan−Meier method and the differences were assessed by the log-rank test.

Multivariable analysis using the Cox proportional hazards model were conducted to evaluate the risk for the primary composite HF end point adjusted by age and sex as model 1. Moreover, we performed multivariable analysis with 9 additional covariates that were statistically significant in univariable analysis or considered clinically relevant (body weight, AF type, heart rate during AF rhythm, hypertension, diabetes, preexisting HF, thromboembolic events, chronic obstructive pulmonary disease, and chronic kidney disease) as model 2. Proportional hazards assumptions for the risk-adjusting variables were assessed on the plots of log (time) versus log [–log(survival)] stratified by the variables and verified to be acceptable. Furthermore, we performed subgroup analyses stratified by those variables with the *P* value for interaction in the Cox proportional hazards models with potential confounders consisting of 11 clinical characteristics on multivariable analysis to examine the heterogeneity in the subgroups. Statistical analyses were performed using JMP 10 (SAS Institute Inc, Cary, NC) software. All tests were 2-tailed and *P* value of <0.05 was considered significant.

RESULTS

Patient Characteristics

Fine fibrillatory wave was observed in 589 patients (24.1%) on baseline ECG. Patients with fine fibrillatory wave were older, and had higher prevalence of sustained AF, low heart rate during AF rhythm, preexisting HF, and chronic kidney disease than those with coarse fibrillatory wave (fine fibrillatory wave versus coarse fibrillatory wave: age 76.1 years versus 73.1 years, *P*<0.001 for age; 66.6% versus 62.1%, *P*=0.048 for sustained AF; 43.0% versus 31.2%, *P*<0.001 for heart rate less than 80 bpm; 32.4% versus 27.5%, *P*=0.02 for preexisting HF; 40.8% versus 33.6%, *P*=0.02 for chronic kidney disease) (Table 1). However, the estimated AF interval and the prevalence of previous thromboembolic events did not differ between the 2 groups (2.5 versus 2.1 years, *P*=0.13; 19.9% versus 16.8%, *P*=0.09). Moreover, CHA_2DS_2-VASc score, left ventricular end-diastolic diameter, left atrial (LA) diameter and cardiothoracic ratio on chest X-ray were higher in patients with fine fibrillatory wave (46.9 versus 44.2 mm, *P*<0.001 for LA diameter). At the time of enrollment, the prevalence of oral anticoagulant did not significantly differ between the 2 groups (55.8% versus 59.6%, *P*=0.11).

The prevalence of fine fibrillatory wave was significantly higher with longer AF interval, lower heart rate during AF rhythm and larger LA diameter in patients with sustained AF, although these relationships were less notable in patients with paroxysmal AF (Figure S1).

Risk for Heart Failure Events in Patients With Fine Fibrillatory Wave

The median follow-up duration was 5.9 (interquartile range, 2.1–8.0) years. The incidence of the primary HF end point of a composite of hospitalization because of HF or cardiac death was significantly higher in patients with fine fibrillatory wave than in those with coarse fibrillatory wave (5.3% versus 3.6% per patient-year, log-rank *P*<0.001) (Table 2, Figure 2). The incidences of each individual component of the primary end point were also significantly higher in patients with fine fibrillatory wave (4.4% versus 3.2% per patient-year, log-rank *P*=0.01 for hospitalization because of HF; 1.5% versus 0.7% per patient-year, *P*<0.001 for cardiac death) (Table 2, Figure S2). The incidence of non-cardiac death in patients with fine fibrillatory wave was also higher (5.3% versus 3.8% per patient-year) (Table 2). The incidence rates (% per patient-year) of clinical outcomes in both groups are shown in Table 2. Even after adjusting for confounders on multivariable

Table 1. Baseline Characteristics

	Fine fibrillatory wave n=589	Coarse fibrillatory wave n=1853	*P* value
Age, y	76.1±10.7	73.1±10.6	<0.001
≥75 y	366 (62.1%)	897 (48.4%)	<0.001
Women	244 (41.4%)	743 (40.1%)	0.57
Body weight, kg	59.1±14.3	59.6±13.3	0.45
<50 kg	146 (26.6%)	420 (25.0%)	0.45
Sustained AF	392 (66.6%)	1150 (62.1%)	0.048
Estimated AF interval, y	2.5 (0.2–7.6) (n=404)	2.1 (0.3–5.7) (n=1338)	0.13
Heart rate during AF rhythm, bpm	92.1±29.8	95.3±26.0	0.01
≥110 bpm	135 (25.3%)	468 (25.3%)	0.15
<80 bpm	253 (43.0%)	578 (31.2%)	<0.001
Hypertension	364 (61.8%)	1146 (61.9%)	0.98
Diabetes	152 (25.8%)	408 (22.0%)	0.06
Preexisting heart failure	191 (32.4%)	510 (27.5%)	0.02
Previous thromboembolic events	117 (19.9%)	311 (16.8%)	0.09
COPD	29 (4.9%)	105 (5.7%)	0.49
Chronic kidney disease	240 (40.8%)	622 (33.6%)	0.02
CHA_2DS_2-VASc score	3.7±1.6	3.3±1.7	<0.001
Echocardiographic findings	(n=488)	(n=1469)	
Left ventricular end-diastolic diameter, mm	47.2±6.7	46.3±6.4	0.01
Left ventricular ejection fraction (%)	62.1±11.1	62.7±11.3	0.31
<40%	23 (4.7%)	80 (5.4%)	0.52
Left atrial diameter, mm	46.9±9.4	44.2±7.9	<0.001
≥50 mm	164 (33.6%)	349 (23.9%)	<0.001
Chest X-ray findings	(n=519)	(n=1581)	
CTR, %	56.6±8.0	54.1±7.2	<0.001
≥60%	176 (33.9%)	343 (21.7%)	<0.001
Laboratory findings			
BNP, pg/dL	114.6 (66.7–259.0) (n=88)	126.9 (48.8–239.3) (n=237)	0.96
NT-pro BNP, pg/dL	835 (397–2096) (n=204)	853 (433–1758) (n=573)	0.74
≥1000 pg/dL	97 (47.6%)	262 (45.7%)	0.65
Medications at the time of enrollment			
Oral anticoagulant	328 (55.8%)	1099 (59.6%)	0.11
Antiplatelet drugs	182 (31.0%)	491 (26.6%)	0.04
Statin	143 (24.3%)	402 (21.8%)	0.20
ACEI/ARB	278 (47.3%)	798 (43.3%)	0.09
Beta blockers	175 (29.8%)	534 (28.9%)	0.70
Verapamil/diltiazem	88 (15.0%)	240 (13.0%)	0.23
Digitalis	108 (18.4%)	255 (13.8%)	0.008
Antiarrhythmic drugs	70 (11.9%)	285 (15.5%)	0.03
Furosemide	224 (38.1%)	506 (27.4%)	<0.001
Mineralocorticoid receptor antagonist	9 (1.5%)	30 (1.6%)	0.87

Categorical variables are presented as numbers (percentage). Continuous variables are presented as the mean±SD except estimated atrial fibrillation interval, brain natriuretic peptide, and NT-proBNP (N-terminal pro brain natriuretic peptide) presented as median (interquartile range) because of their distributions.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CTR, cardiothoracic ratio; and NT-proBNP, N-terminal pro brain natriuretic peptide.

Table 2. Incidences of Heart Failure End Points

	Overall No. of patients with events (% per patient-y)	With fine fibrillatory wave No. of patients with events (% per patient-y)	With coarse fibrillatory wave No. of patients with events (% per patient-y)
Primary composite heart failure end point: a composite of hospitalization because of heart failure or cardiac death	460 (4.0%)	138 (5.3%)	322 (3.6%)
Secondary end point			
Hospitalization because of heart failure	407 (3.5%)	113 (4.4%)	294 (3.2%)
All-cause death	637 (5.0%)	199 (6.8%)	438 (4.5%)
Non-cardiac death	524 (4.1%)	155 (5.3%)	369 (3.8%)
Cardiac death	113 (0.9%)	44 (1.5%)	69 (0.7%)

analysis, the higher risk associated with fine fibrillatory wave for the primary composite HF end point remained significant (model 1: hazard ratio, 1.32; 95% CI, 1.08–1.61; *P*=0.007; model 2: hazard ratio, 1.31, 95% CI, 1.07–1.61; *P*=0.01) (Table 3). No statistically significant interaction was observed between hazard ratios for the primary composite HF end point associated with the fine fibrillatory wave and the clinically relevant subgroups (Figure S3), even though the risk was neutral in patients with a higher heart rate (≥110 bpm).

Subgroup Analysis of AF With Preexisting HF

A total of 28.7% of study patients had preexisting HF at the time of enrollment. The prevalence of preexisting HF was significantly lower in patients with AF with fine fibrillatory wave than in those with coarse AF (32.4% versus 27.5%, *P*=0.02). The incidence of the primary composite HF end point was significantly higher in patients with AF with fine fibrillatory wave for both those with and without preexisting HF (with preexisting HF: 58.5% versus 49.3%, log-rank *P*=0.04; without preexisting HF: 22.9% versus 15.4%, log-rank *P*=0.006) (Figure S4). Among patients with preexisting HF, there was no significant interaction about the higher risk of fine fibrillatory wave between HF with reduced LVEF and HF with preserved LVEF.

DISCUSSION

The main findings of the current study are as follows: (1) fine fibrillatory wave was associated with advanced age, sustained AF, preexisting HF, and large LA size; (2) fine fibrillatory wave was associated with a higher risk for a composite of hospitalization attributable to HF or cardiac death; (3) the higher risk of fine fibrillatory wave for the primary composite HF end point remained significant even after adjusting for potential confounders.

Several studies reported an association of fine fibrillatory wave with large LA size and impaired LA function,[2] but others did not support such an association.[3,9] In the current study, patients with fine AF had a larger LA and left ventricular size. Moreover, fine AF was more prevalent in sustained AF, but fine AF was also observed in approximately one third of paroxysmal patients with AF . Li et al reported that fine fibrillatory wave is associated with a significantly lower LA appendage ejection fraction and higher spontaneous contrast echo contrast than coarse fibrillatory wave regardless of comparable LVEF and LA diameter.[3] Nakagawa et al also reported a significantly lower LA appendage peak flow velocity in patients with fine fibrillatory wave.[5] Furthermore, Yin et al demonstrated a significant inverse correlation between the amplitude

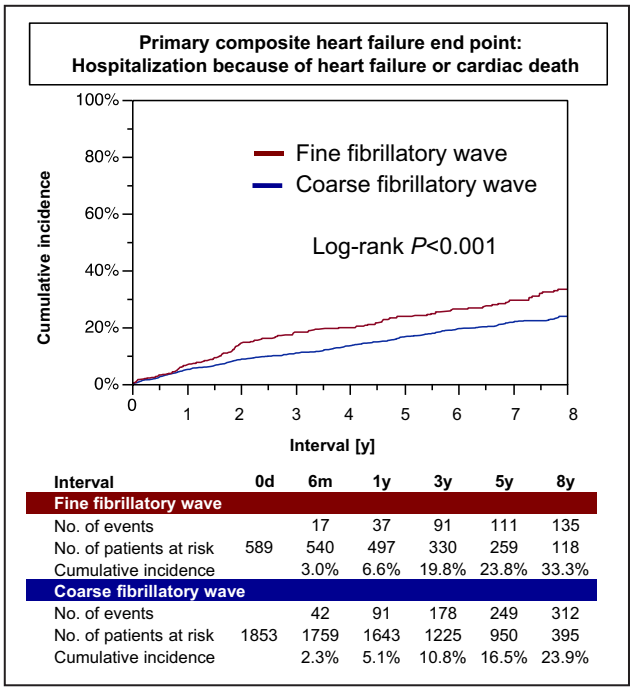


Figure 2. Kaplan–Meier curves for the primary composite heart failure end point (composite of hospitalization because of heart failure or cardiac death) in patients with fine and coarse fibrillatory wave.

of fibrillatory wave and the size of low voltage area in the LA.[8] Based on these studies, fine fibrillatory wave may represent the presence of more advanced atrial dysfunction with negative remodeling.

Regarding the association between AF and HF, AF is a progressive disease with negative remodeling of the atrium and ventricle, which is caused by the loss of atrial kick, irregular frequent ventricular response, and impaired diastolic function.[10] Conversely, HF also increases the incidence of AF, especially at the time of acute exacerbation and dehydration. Thus, AF begets HF and vice versa, leading to increased mortality and morbidities.[10–12] To the best of our knowledge, the current study is the first to reveal the higher risk of fine fibrillatory wave for HF in patients with AF compared with coarse fibrillatory wave. Recently, LA function was reported to be important for the development and exacerbation of HF.[13] Of note, decreased LA function represented by fine fibrillatory wave was also associated with a higher risk for HF in patients with AF lacking atrial kick. Consistent with our study, King et al reported that severe atrial fibrosis detected by late gadolinium enhancement-cardiac magnetic resonance imaging is associated with increased adverse clinical outcomes, including HF, stroke, and death.[14] Recently, the prognostic impact of AF in patients with HF has been recognized as different according to types of AF or HF.[15-17] However, the current study showed that patients with AF with fine fibrillatory wave had higher risk of HF events than coarse fibrillatory wave regardless of the presence of HF or the type of AF. Based on the current study and these studies, fine fibrillatory wave during AF rhythm may be helpful to clinicians as a simple and

Table 3. Independent Risk Factors for the Primary Composite Heart Failure End Point: The Cox Proportional Hazards Model

	Univariable analysis			Model 1 Multivariable analysis			Model 2 Multivariable analysis		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Fine fibrillatory wave	1.48	1.21–1.80	<0.001	1.32	1.08–1.61	0.007	1.31	1.07–1.61	0.01
Age, per y	1.06	1.05–1.08	<0.001	1.06	1.05–1.08	<0.001	1.04	1.03–1.05	<0.001
Women	1.31	1.09–1.57	0.004	1.01	0.83–1.22	0.93	0.88	0.69–1.11	0.28
Body weight, per kg	0.98	0.97–1.02	<0.001				0.99	0.98–0.99	0.03
Sustained AF	1.72	1.41–2.12	<0.001				1.21	0.95–1.54	0.23
Heart rate, per bpm	1.00	0.99–1.00	0.009				1.00	0.99–1.01	0.51
Hypertension	1.35	1.11–1.65	0.002				1.22	0.99–1.51	0.06
Diabetes	1.46	1.19–1.77	<0.001				1.37	1.11–1.69	0.004
Preexisting heart failure	4.14	3.45–4.99	<0.001				3.20	2.61–3.93	<0.001
Previous ischemic stroke/systemic embolism	1.46	1.16–1.82	0.002				1.29	1.02–1.62	0.03
COPD	1.61	1.10–2.27	0.02				1.25	0.85–1.77	0.25
Chronic kidney disease	2.32	1.93–2.79	<0.001				1.39	1.14–1.70	0.001

Model 1: adjustment by age and sex. Model 2: adjustment by 11 covariates that was statistically significant in univariable analysis or considered clinically relevant (age, sex, body weight, atrial fibrillation type, heart rate during atrial fibrillation rhythm, hypertension, diabetes, preexisting heart failure, thromboembolic events, chronic obstructive pulmonary disease, and chronic kidney disease). AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.

quick sign to evaluate HF risk in patients with AF. Given that fine fibrillatory wave is a marker for more advanced atrial fibrosis, patients with AF with fine fibrillatory wave may require more careful management.

Although no statistically significant interaction was observed between hazard ratios for the primary composite HF end point in all major subgroups of the current study, its significance was lower in patients with AF with a heart rate ≥110 bpm. As the heart rate during AF is regulated by the atrioventricular node, a high heart rate may reflect the absence of atrioventricular-node dysfunction indicating extensive atrial degeneration in the right atrium. The clinical significance of fine fibrillatory wave in patients with AF with a high heart rate warrants further investigation.

Limitations

There are several limitations in the current study. First, there was unavoidable selection bias considering the availability of baseline ECG data in the registry. As we previously reported, the incidence of a composite of cardiac death, myocardial infarction or hospitalization because of HF was significantly higher in patients with AF whose ECG data were available than in those whose ECG data were not available in this registry.[1] The higher risk for subsequent cardiac events in the study patients relative to the excluded patients may have influenced the study results. Second, the amplitude of the fibrillatory wave was manually measured by only 1 cardiologist. Therefore, measurement bias including the influence of fluctuation of baseline and/or QRS/T wave especially in patients with high heart rate might occur. Third, all patients were Japanese in this study; therefore, caution is needed in generalizing the results of the current study to populations outside Japan. Lastly, the multivariable analyses may not have sufficiently eliminated the influence of unmeasured confounders.

CONCLUSIONS

In a Japanese community-based prospective survey, fine fibrillatory wave was more prevalent in patients with a larger LA diameter or in those with sustained AF compared with coarse fibrillatory wave and was independently associated with a higher risk for HF events.

ARTICLE INFORMATION

Received October 13, 2021; accepted February 21, 2022.

Affiliations

Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto, Japan (T.K., M.K., T.Y., S.M.); Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan (T.K.); and Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan (H.O., Y.H., M. Abe, M. Akao).

Acknowledgments

We sincerely appreciate all the members of the Fushimi AF Registry, and Dr H. Sugiyama (Department of Cardiovascular Medicine, Kyoto Prefectural University of Medicine) for his expertise in ECG analysis and our clinical research coordinators (T. Shinagawa, M. Mitamura, M. Fukahori, M. Kimura, M. Fukuyama, C. Kamata and N. Nishiyama). Author Contributions: 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 data analysis. T.K. analyzed the data and wrote the paper. H.O., Y.H., M. Abe, and M. Akao contributed to the acquisition of data and helped with data analysis and interpretation. H.O., Y.H., M.K., T.Y., and S.M. contributed to the statistical analysis. M. Akao is a principal investigator of the Fushimi AF Registry and the corresponding author of this paper.

Sources of Funding

The Fushimi AF Registry is supported by research funding from Boehringer Ingelheim, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Astellas Pharma, AstraZeneca, Daiichi Sankyo, Novartis Pharma, MSD, Sanofi-Aventis, and Takeda Pharmaceutical. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. This study was partially supported by the Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes Mellitus from Japan Agency for Medical Research and Development, AMED (19ek0210082h0003 and 18ek0210056h0003).

Disclosures

Dr Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1
Figures S1–S4

REFERENCES

1. Kawaji T, Ogawa H, Hamatani Y, Kato M, Yokomatsu T, Miki S, Abe M, Akao M. Association of inverted T wave during atrial fibrillation rhythm with subsequent cardiac events. *Heart*. 2022;108:178–185. doi: 10.1136/heartjnl-2021-319199
2. Aysha MH, Hassan AS. Diagnostic importance of fibrillatory wave amplitude: a clue to echocardiographic left atrial size and etiology of atrial fibrillation. *J Electrocardiol*. 1988;21:247–251. doi: 10.1016/0022-0736(88)90099-4
3. Li Y-H, Hwang J-J, Tseng Y-Z, Kuan P, Lien W-P. Clinical significance of fibrillatory wave amplitude. *Chest*. 1995;108:359–363. doi: 10.1378/chest.108.2.359
4. İçen YK, Koca H, Sümbül HE, Yıldırım A, Koca F, Yıldırım A, Ardıc ML, Coşkun M, Uğurlu M, Koç M. Relationship between coarse F waves and thromboembolic events in patients with permanent atrial fibrillation. *J Arrhythm*. 2020;36:1025–1031. doi: 10.1002/joa3.12430
5. Nakagawa K, Hirai T, Shinokawa N, Uchiyama Y, Kameyama T, Takashima S, Fujiki A, Asanoi H, Inoue H. Relation of fibrillatory wave amplitude with hemostatic abnormality and left atrial appendage dysfunction in patients with chronic nonrheumatic atrial fibrillation. *Circ J*. 2001;65:375–380. doi: 10.1253/jcj.65.375
6. Mutlu B, Karabulut M, Eroglu E, Tigen K, Bayrak F, Fotbolcu H, Basaran Y. Fibrillatory wave amplitude as a marker of left atrial and left atrial appendage function, and a predictor of thromboembolic risk in patients with rheumatic mitral stenosis. *Int J Cardiol*. 2003;91:179–186. doi: 10.1016/S0167-5273(03)00024-X
7. Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, Hasegawa K, Tsuji H, Furuke K. 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. doi: 10.1016/j.jjcc.2012.12.002
8. Yin R, Fu Y, Yang Z, Li B, Pen J, Zheng Z. Fibrillatory wave amplitude on transesophageal ECG as a marker of left atrial low-voltage areas in patients with persistent atrial fibrillation. *Ann Noninvasive Electrocardiol*. 2017;22:e12421. doi: 10.1111/anec.12421

9. Morganroth J, Horowitz LN, Josephson ME, Kastor JA. Relationship of atrial fibrillatory wave amplitude to left atrial size and etiology of heart disease. An old generalization re-examined. *Am Heart J*. 1979;97:184–186. doi: 10.1016/0002-8703(79)90354-5
10. Santhanakrishnan R, Wang NA, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614
11. Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, Theuns DA, Jordaens L, Komajda M, Follath F, Swedberg K, Cleland JG. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the Euroheart Failure Survey. *Eur Heart J*. 2008;29:1618–1624. doi: 10.1093/eurheartj/ehn217
12. Bajaj NS, Bhatia V, Sanam K, Ather S, Hashim T, Morgan C, Fonarow GC, Nanda NC, Prabhu SD, Adamopoulos C, et al. Impact of atrial fibrillation and heart failure, independent of each other and in combination, on mortality in community-dwelling older adults. *Am J Cardiol*. 2014;114:909–913. doi: 10.1016/j.amjcard.2014.05.045
13. Deferm S, Martens P, Verbrugge FH, Bertrand PB, Dauw J, Verhaert D, Dupont M, Vandervoort PM, Mullens W. LA mechanics in decompensated heart failure. *JACC: Cardiovasc Imag*. 2020;13:1107–1115. doi: 10.1016/j.jcmg.2019.12.008
14. King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT, Chelu MG, Silver MA, Biskupiak J, Wilson BD, et al. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. *J Am Coll Cardiol*. 2017;70:1311–1321. doi: 10.1016/j.jacc.2017.07.758
15. Yamauchi T, Sakata Y, Miura M, Tadaki S, Ushigome R, Sato K, Onose T, Tsuji K, Abe R, Oikawa T, et al. Prognostic impact of new-onset atrial fibrillation in patients with chronic heart failure – a report from the CHART-2 study –. *Circ J*. 2016;80:157–167. doi: 10.1253/circj.CJ-15-0783
16. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, et al. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70:2490–2500. doi: 10.1016/j.jacc.2017.09.027
17. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, et al. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J*. 2018;39:4277–4284. doi: 10.1093/eurheartj/ehy626

SUPPLEMENTAL MATERIAL

Working group members of the FUSHIMI AF Registry

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

Steering Committee: Esato M (Ijinkai Takeda General Hospital), Abe M (National Hospital Organization Kyoto Medical Center), Tsuji H (Tsuji Clinic), Furuke K (Furuke Clinic).

Statistical Analysis: Wada H (National Hospital Organization Kyoto Medical Center).

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).

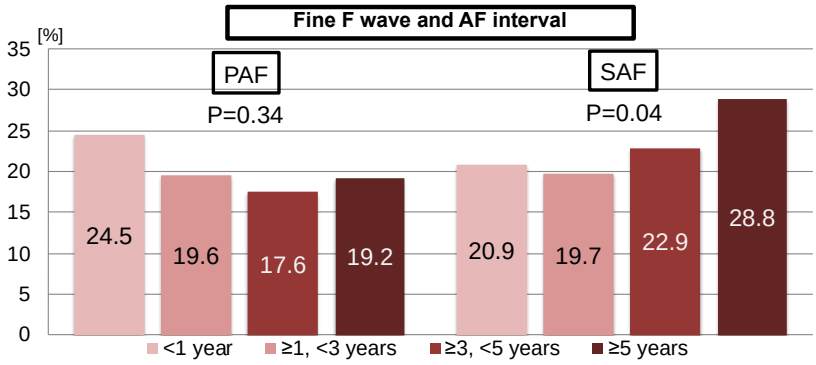
Clinical Event Committee: Kawabata Y, Yasuda K, Kameyama K (National Hospital Organization Kyoto Medical Center).

Participating institutions: Department of Cardiology, National Hospital Organization Kyoto Medical Center (Akao M, Abe M, Ogawa H, Masunaga N, Iguchi M, Ishii M, An Y, Unoki T, Niki S, Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Tezuka Y, Doi K, Aono Y, Ikeda S, Osakada G, Nakashima Y, Kanasaki M, Nakano T, Funatsu J, Nishio M, Takenaka Y); Department of Arrhythmia, Ijinkai Takeda General Hospital (Chun YH, Esato M, Kida Y, Nishina N); Koujinkai Oshima Hospital (Terada K); Division of Translational Research, National Hospital Organization Kyoto Medical Center (Hasegawa K, Wada H); Kanai Hospital (Nishio M, Kamiya Y, Abe M, Ishii M); Tsuji clinic (Tsuji H); Furukawa Medical Clinic (Furukawa K); Nishikawa Clinic (Nishikawa M); Taniguchi Clinic (Taniguchi Y); Gushiken Clinic (Gushiken T); Kyoto Rehabilitation Hospital (Hirata Y); Yoda Clinic (Yoda J); Tasato Clinic (Tasato H); Ogawa Medical Office (Ogawa T); Mukaijima Hospital (Wakatsuki Y, Yahata M, Higashitani N); Itoh Hemodialysis Clinic (Itoh H); Itoh Clinic (Itoh H, Ohmori Y); Ryokuhoukai Tsuji Clinic (Tsuji K); Kitamura Clinic (Kitamura S); Izumikawa Clinic (Izumikawa F); Hirota Clinic (Hirota N); Kyomachi-Oota Clinic (Oota K); Kouseikai Rehabilitation Clinic (Kou K); Inariyama Takeda Hospital (Tanaka T, Iguchi M); Matsushita Clinic (Matsushita N); Kitani Clinic (Kitani K); Kimura Clinic (Kimura F); Hayashi Clinic (Hayashi S); Handa Clinic (Handa S); Soseikai General Hospital (Hasegawa S, Kono T, Otsuka K, Soyama A, Okamoto J, Nakai Y); Asamoto Clinic (Asamoto H); Sugano Clinic (Tanaka H, Murata T); Fushimi Momoyama General Hospital (Kayawake S, Kinoshita Y); Furuke Clinic (Furuke K); Kanehisa Clinic (Asano N); Tahara Clinic (Tahara K); Matsumoto Medical Office

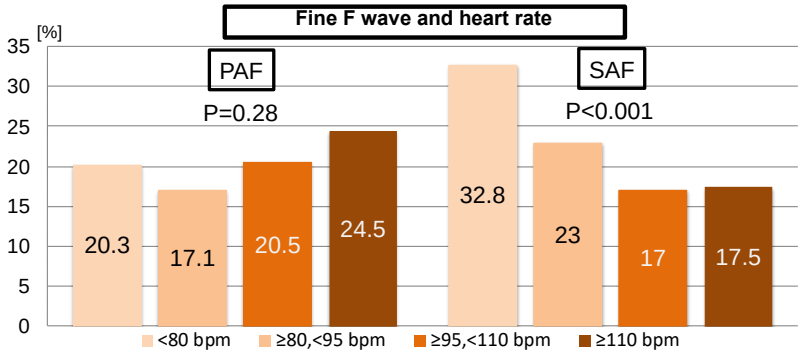
(Matsumoto K); Kuroda Clinic (Kuroda O); Ochiai Clinic (Ochiai K, Ochiai J); Fujii Clinic (Fujii M); Kurihara Clinic (Kurihara M); Kuzuyama Clinic (Ito A); Kenkokai Fushimi Clinic (Totsuzaki S); Nakayama Orthopedic Clinic (Nakayama H); Department of Cardiovascular Medicine, Ijinkai Takeda General Hospital (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).

Figure S1. The prevalence of fine fibrillatory (F) wave according to baseline risks in PAF and SAF.

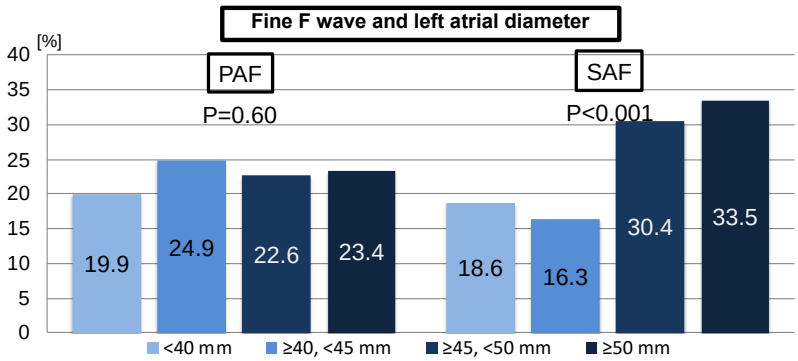
A) AF interval



B) Heart rate during AF rhythm



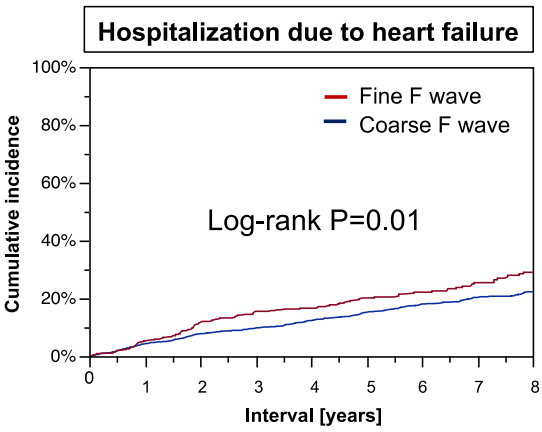
C) Left atrial diameter



AF=atrial fibrillation, PAF=paroxysmal atrial fibrillation, SAF=sustained atrial fibrillation

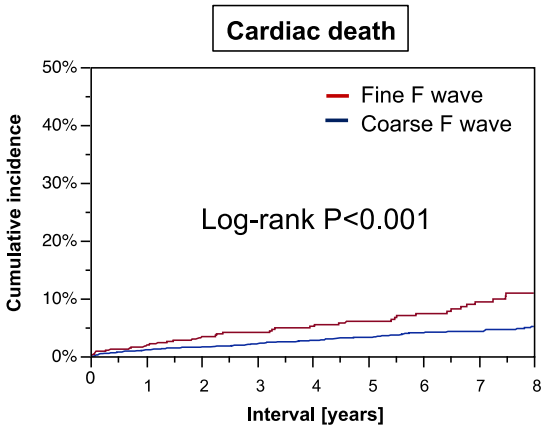
Figure S2. Kaplan-Meier curves for individual components of the composite heart failure endpoint between patients with fine and coarse F wave.

A) Hospitalization due to heart failure



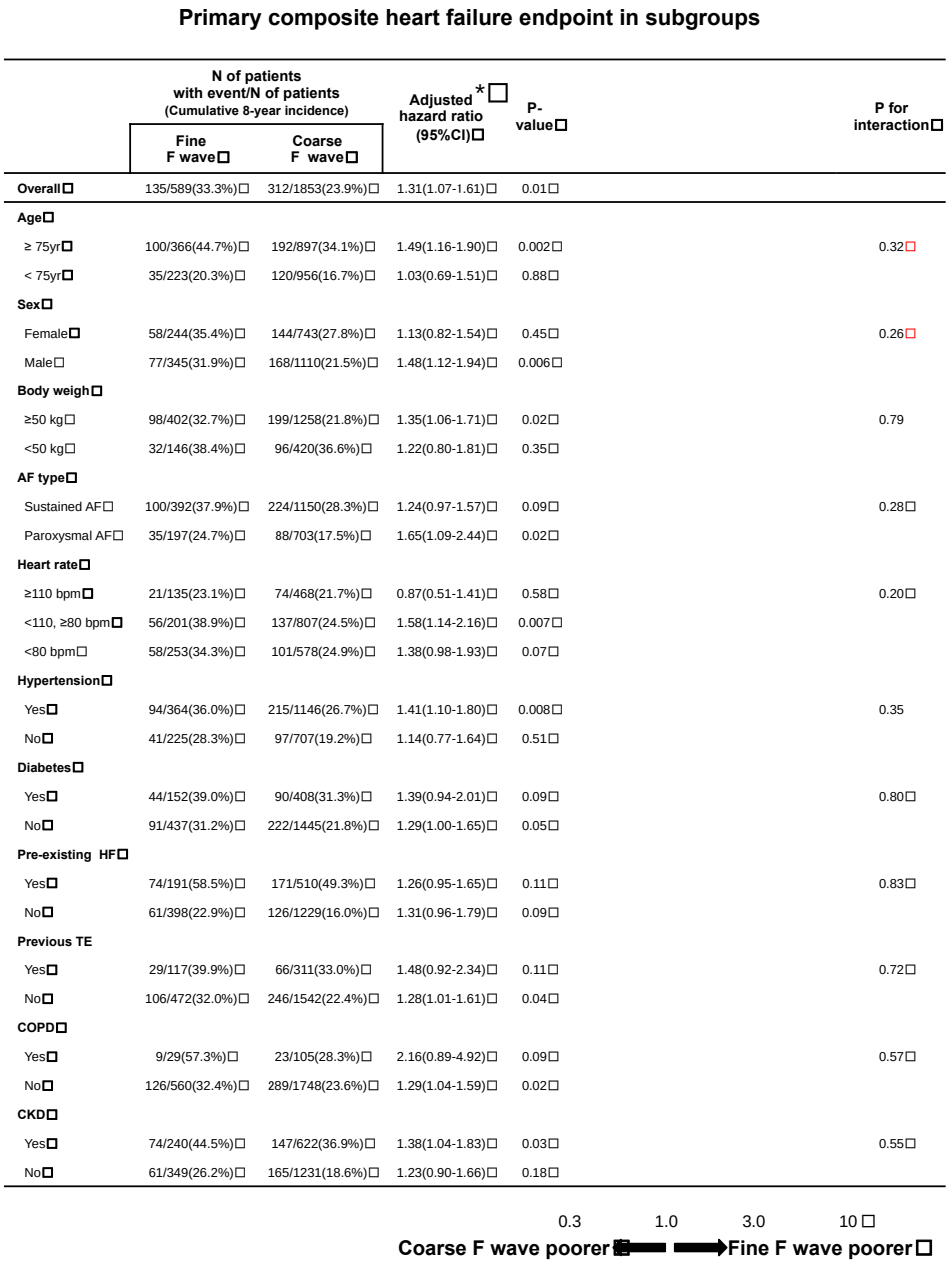
Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		10	29	75	91	112
N of patients at risk	589	540	497	330	259	118
Cumulative incidence		1.8%	5.3%	15.5%	20.1%	29.0%
Coarse F wave						
N of events		31	77	159	225	286
N of patients at risk	1853	1759	1643	1225	950	395
Cumulative incidence		1.7%	4.3%	9.7%	15.1%	22.5%

B) Cardiac death



Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		7	10	21	28	40
N of patients at risk	589	549	521	380	308	147
Cumulative incidence		1.2%	1.8%	4.1%	6.0%	10.9%
Coarse F wave						
N of events		13	20	35	49	64
N of patients at risk	1853	1785	1704	1318	1071	472
Cumulative incidence		0.7%	1.1%	2.1%	3.3%	5.1%

Figure S3. Subgroup analysis for the primary composite heart failure endpoint.

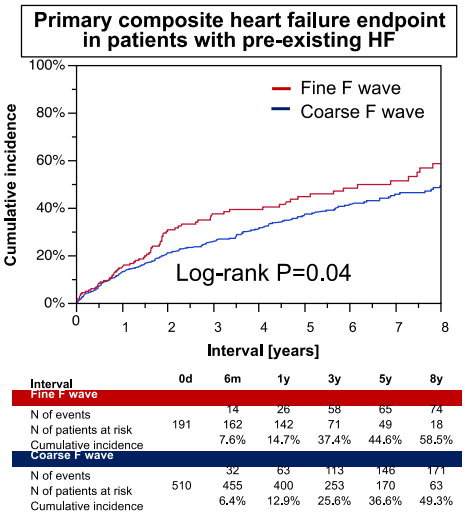


*adjusted by 11 covariates that were statistically significant in univariable analysis or considered clinically relevant (age, sex, body weight, AF type, heart rate during AF rhythm, hypertension, diabetes, pre-existing HF, TE, COPD and CKD)

AF=atrial fibrillation; CI=confidence interval; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; F=fibrillatory; HF=heart failure; TE=thromboembolic events

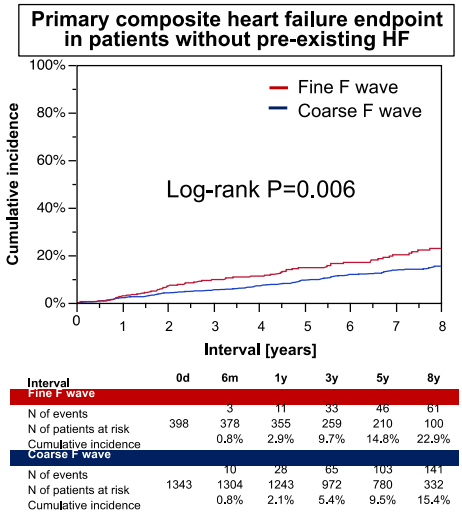
Figure S4. Subgroup analysis for the primary composite heart failure endpoint (composite of hospitalization due to heart failure or cardiac death).

A) Kaplan-Meier curve in patients with pre-existing HF



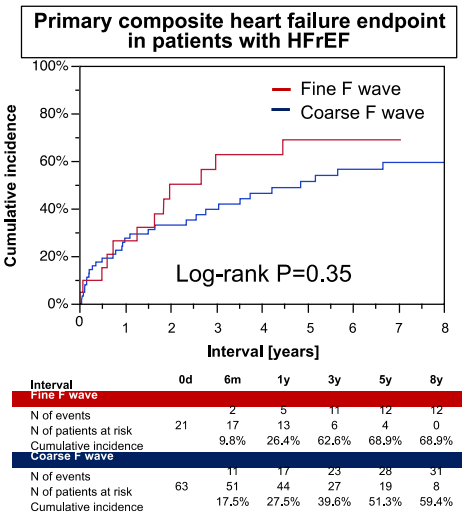
Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		14	26	58	65	74
N of patients at risk	191	162	142	71	49	18
Cumulative incidence		7.6%	14.7%	37.4%	44.6%	58.5%
Coarse F wave						
N of events		32	63	113	146	171
N of patients at risk	510	455	400	253	170	63
Cumulative incidence		6.4%	12.9%	25.6%	36.6%	49.3%

B) Kaplan-Meier curve in patients without pre-existing HF



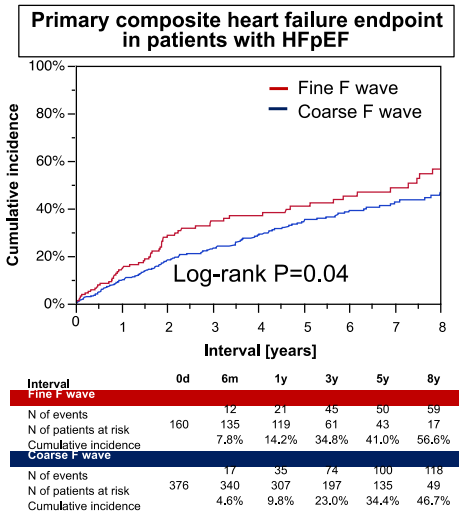
Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		3	11	33	46	61
N of patients at risk	398	378	355	259	210	100
Cumulative incidence		0.8%	2.9%	9.7%	14.8%	22.9%
Coarse F wave						
N of events		10	28	65	103	141
N of patients at risk	1343	1304	1243	972	780	332
Cumulative incidence		0.8%	2.1%	5.4%	9.5%	15.4%

C) Kaplan-Meier curve in patients with HFrEF



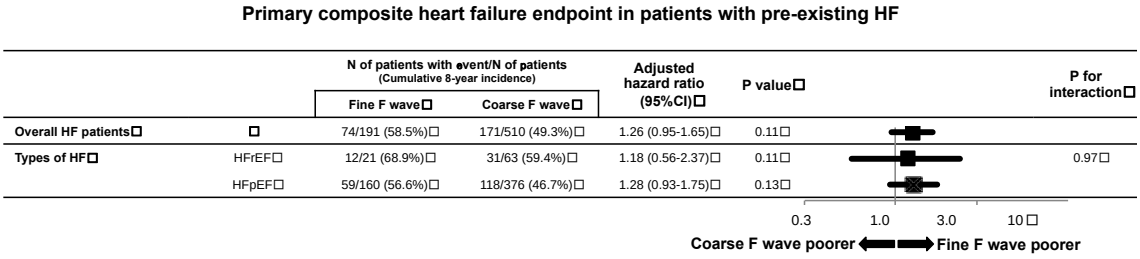
Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		2	5	11	12	12
N of patients at risk	21	17	13	6	4	0
Cumulative incidence		9.8%	26.4%	62.6%	68.9%	68.9%
Coarse F wave						
N of events		11	17	23	28	31
N of patients at risk	63	51	44	27	19	8
Cumulative incidence		17.5%	27.5%	39.6%	51.3%	59.4%

D) Kaplan-Meier curve in patients with HFpEF



Interval	0d	6m	1y	3y	5y	8y
Fine F wave						
N of events		12	21	45	50	59
N of patients at risk	160	135	119	61	43	17
Cumulative incidence		7.8%	14.2%	34.8%	41.0%	56.6%
Coarse F wave						
N of events		17	35	74	100	118
N of patients at risk	376	340	307	197	135	49
Cumulative incidence		4.6%	9.8%	23.0%	34.4%	46.7%

E) Subgroup analysis of the types of HF among patients with pre-existing HF



HF=heart failure; HFpEF=heart failure with preserved left ventricular ejection fraction; HFrEF=heart failure with reduced left ventricular ejection fraction