ORIGINAL RESEARCH

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

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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...
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

**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.

**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 Jinkai 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
presented as the mean with SD or median with inter-quartile 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 \( \log(\text{time}) \) versus \( \log[-\log(\text{survival})] \) 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, CHA2DS2-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 (6.7%)                      | 0.49    |
| Chronic kidney disease         | 240 (40.8%)                 | 622 (33.6%)                     | 0.02    |
| CHA2DS2-VASc score             | 3.7±1.6                     | 3.3±1.7                         | <0.001  |
| Echocardiographic findings     |                             |                                 |         |
| 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           |                             |                                 |         |
| 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    |

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.
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 (\( \geq 110 \) 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.\(^5\) 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
of fibrillatory wave and the size of low voltage area in the LA.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14} Recently, the prognostic impact of AF in patients with HF has been recognized as different according to types of AF or HF.\textsuperscript{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**

| Variables                              | Univariable analysis | Model 1 Multivariable analysis | Model 2 Multivariable analysis |
|----------------------------------------|----------------------|--------------------------------|--------------------------------|
|                                        | 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. 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.

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

A) AF interval

![AF interval graph]

B) Heart rate during AF rhythm

![Heart rate graph]

C) Left atrial diameter

![Left atrial diameter graph]

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

B) Cardiac death

| Interval [years] | 0d | 6m | 1y | 2y | 3y | 5y | 8y |
|------------------|----|----|----|----|----|----|----|
| **Fine F wave**  |    |    |    |    |    |    |    |
| N of events      | 589| 540| 487| 330| 259| 112|    |
| N of patients at risk | 589| 540| 487| 330| 259| 112|    |
| Cumulative incidence | 1.8%| 5.3%| 15.5%| 20.1%| 20.0%|    |    |

| Interval [years] | 0d | 6m | 1y | 2y | 3y | 5y | 8y |
|------------------|----|----|----|----|----|----|----|
| **Coarse F wave** |    |    |    |    |    |    |    |
| N of events      | 31 | 77 | 159| 225| 225| 289|    |
| N of patients at risk | 1853| 1759| 1643| 1225| 900| 396|    |
| Cumulative incidence | 1.7%| 4.3%| 9.7%| 15.1%| 22.5%|    |    |

Log-rank P = 0.01

| Interval [years] | 0d | 6m | 1y | 2y | 3y | 5y | 8y |
|------------------|----|----|----|----|----|----|----|
| **Fine F wave**  |    |    |    |    |    |    |    |
| N of events      | 589| 549| 521| 360| 308| 147|    |
| N of patients at risk | 589| 549| 521| 360| 308| 147|    |
| Cumulative incidence | 1.2%| 1.8%| 4.1%| 6.0%| 10.9%|    |    |

Log-rank P < 0.001

| Interval [years] | 0d | 6m | 1y | 2y | 3y | 5y | 8y |
|------------------|----|----|----|----|----|----|----|
| **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.

**Primary composite heart failure endpoint in subgroups**

|                        | N of patients with event/N of patients (Cumulative 8-year incidence) | Adjusted hazard ratio (95% CI) | P-value | P for interaction |
|------------------------|---------------------------------------------------------------------|-------------------------------|---------|------------------|
| **Fine F wave**        |                                                                     |                               |         |                  |
| Overall                | 135/589(23.3%)                                                     | 1.31(1.07-1.61)               | 0.01    |                  |
| **Coarse F wave**      |                                                                     |                               |         |                  |
| **Age**                |                                                                     |                               |         |                  |
| ≥ 75yr                 | 100(360)(44.7%)                                                     | 1.49(1.16-1.90)               | 0.002   | 0.32             |
| < 75yr                 | 35(223)(30.3%)                                                     | 1.03(0.69-1.51)               | 0.88    |                  |
| **Sex**                |                                                                     |                               |         |                  |
| Female                 | 58(244)(25.4%)                                                     | 1.13(0.62-1.54)               | 0.45    | 0.26             |
| Male                   | 77(345)(31.9%)                                                     | 1.40(1.12-1.74)               | 0.006   |                  |
| **Body weight**        |                                                                     |                               |         |                  |
| ≥50 kg                 | 98(402)(32.7%)                                                     | 1.35(1.06-1.71)               | 0.02    | 0.79             |
| <50 kg                 | 32(146)(38.4%)                                                     | 1.22(0.90-1.61)               | 0.35    |                  |
| **AF type**            |                                                                     |                               |         |                  |
| Sustained AF           | 100(392)(37.9%)                                                    | 1.24(0.97-1.57)               | 0.09    | 0.28             |
| Paroxysmal AF          | 35(197)(24.7%)                                                     | 1.05(0.89-1.24)               | 0.42    |                  |
| **Heart rate**         |                                                                     |                               |         |                  |
| ≥110 bpm               | 21(135)(23.1%)                                                     | 0.87(0.51-1.41)               | 0.58    | 0.20             |
| <110, ≥80 bpm          | 56(201)(38.9%)                                                     | 1.56(1.14-2.16)               | 0.007   |                  |
| <80 bpm                | 58(253)(34.3%)                                                     | 1.38(0.96-1.93)               | 0.07    |                  |
| **Hypertension**       |                                                                     |                               |         |                  |
| Yes                    | 94(346)(30.6%)                                                     | 1.41(1.10-1.80)               | 0.008   | 0.35             |
| No                     | 41(225)(28.3%)                                                     | 1.14(0.77-1.64)               | 0.51    |                  |
| **Diabetes**           |                                                                     |                               |         |                  |
| Yes                    | 44(152)(39.9%)                                                     | 1.39(0.94-2.01)               | 0.09    | 0.80             |
| No                     | 91(437)(31.2%)                                                     | 1.29(1.00-1.65)               | 0.05    |                  |
| **Pre-existing HF**    |                                                                     |                               |         |                  |
| Yes                    | 74(191)(39.8%)                                                     | 1.26(0.95-1.65)               | 0.11    | 0.63             |
| No                     | 61(398)(22.9%)                                                     | 1.51(1.06-1.79)               | 0.09    |                  |
| **Previous TE**        |                                                                     |                               |         |                  |
| Yes                    | 29(117)(29.9%)                                                     | 1.48(0.92-2.34)               | 0.11    | 0.72             |
| No                     | 106(472)(22.9%)                                                    | 1.28(1.01-1.61)               | 0.04    |                  |
| **COPD**               |                                                                     |                               |         |                  |
| Yes                    | 9(29)(57.3%)                                                       | 2.16(0.89-4.93)               | 0.09    | 0.57             |
| No                     | 126(503)(23.4%)                                                    | 1.29(1.04-1.59)               | 0.02    |                  |
| **CKD**                |                                                                     |                               |         |                  |
| Yes                    | 74(249)(44.5%)                                                     | 1.38(1.04-1.83)               | 0.03    | 0.55             |
| No                     | 61(349)(26.2%)                                                     | 1.23(0.90-1.65)               | 0.18    |                  |

*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

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

C) Kaplan-Meier curve in patients with HFrEF

D) Kaplan-Meier curve in patients with HFpEF

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

| N of patients with event/N of patients (Cumulative 8-year incidence) | Adjusted hazard ratio (95% CI) | P value | P for interaction |
|---|---|---|---|
| Overall HF patients | 74/191 (56.2%) | 171/115 (49.3%) | 1.02 (0.29-3.45) | 0.91 | 0.5 |
| Types of HF | | | | | |
| HFrEF | 12/21 (58.6%) | 29/42 (59.4%) | 1.18 (0.36-3.97) | 0.11 | 0.07 |
| HFpEF | 62/170 (36.7%) | 188/276 (67.7%) | 1.29 (0.39-4.50) | 0.27 | 0.3 |

Coarse F wave poorer: Fine F wave poorer
HF=heart failure; HFpEF=heart failure with preserved left ventricular ejection fraction; HFrEF=heart failure with reduced left ventricular ejection fraction