Prognostic Impact of Atrial Fibrillation and New Risk Score of Its Onset in Patients at High Risk of Heart Failure

— A Report From the CHART-2 Study —

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Background: The prognostic impact of atrial fibrillation (AF) among patients at high risk for heart failure (HF) remains unclear. In addition, there is no risk estimation model for AF development in these patients.

Methods and Results: The present study included 5,382 consecutive patients at high risk of HF enrolled in the CHART-2 Study (n=10,219). At enrollment, 1,217 (22.6%) had AF, and were characterized, as compared with non-AF patients, by higher age, lower estimated glomerular filtration rate, higher B-type natriuretic peptide (BNP) level and lower left ventricular ejection fraction. A total of 116 non-AF patients (2.8%) newly developed AF (new AF) during the median 3.1-year follow-up. AF at enrollment was associated with worse prognosis for both all-cause death and HF hospitalization (adjusted hazard ratio (aHR) 1.31, P=0.027 and aHR 1.74, P=0.001, for all-cause death and HF hospitalization, respectively) and new AF was associated with HF hospitalization (aHR 4.54, P<0.001). We developed a risk score with higher age, smoking, pulse pressure, lower eGFR, higher BNP, aortic valvular regurgitation, LV hypertrophy, and left atrial and ventricular dilatation on echocardiography, which effectively stratified the risk of AF development with excellent accuracy (AUC 0.76).

Conclusions: These results indicated that AF is associated with worse prognosis in patients at high risk of HF, and our new risk score may be useful to identify patients at high risk for AF onset.

Key Words: Atrial fibrillation; Heart failure; Prognosis; Risk score

Atrial fibrillation (AF) is a common arrhythmia that affects approximately 1.0% of the general population.[1–3] Furthermore, the prevalence of AF is higher in elderly people and has been increasing with global aging.[1–4] AF is also an independent predictor of death, heart failure (HF) and stroke,[5–8] although appropriate therapy, such as anticoagulation, improves the prognosis of patients.[9,10] Patients with chronic HF (CHF) have a markedly higher prevalence of AF (17–38%) than the general population.[11–13] We recently reported that approximately 35% of patients with Stage C/D HF had AF as a comorbidity and that new-onset AF, but not AF at enrollment, was associated with worse prognosis in HF patients, especially in the first year after onset.[11] However, the prognostic impact of AF among patients with CHF is still controversial.[11–13]
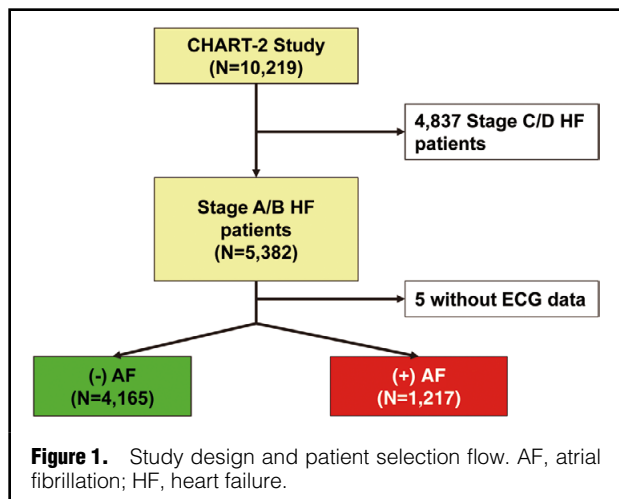
The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have recommended classifying HF patients into Stages A/B/C/D based on the stage of progression.[14] Stage A HF corresponds to patients with a high risk of HF without structural heart disease, Stage B HF is used to classify patients with structural heart disease but without symptomatic HF, and Stages C/D correspond to symptomatic HF.[14] AF is associated with worse prognosis among the general population and patients with coronary artery disease (CAD).[5–8,15] In addition, it was previously reported that new-onset AF is associated with increased incidence of subsequent HF in the general population,[16] indicating that AF in Stage A/B HF patients is an important risk factor for HF exacerbation. Thus, prevention and early identification of AF may help to prevent HF progression, particularly among

Figure 1. Study design and patient selection flow. AF, atrial fibrillation; HF, heart failure.

those in Stage A/B. However, the prognostic impact of AF in patients with Stage A/B HF remains to be elucidated.

Paroxysmal AF (pAF) and non-paroxysmal AF (npAF) are associated with similar risks for stroke.[17] Using mobile cardiac outpatient telemetry, AF was detected in 23% of patients with cryptogenic stroke.[18] Thus, the detection of paroxysmal or asymptomatic AF is clinically important; however, these conditions are often overlooked in regular clinical evaluations, including medical examination, ECG and/or laboratory analysis. Although long-term ECG recordings are useful for detecting AF, they are usually used for screening of AF in patients with suspected symptoms. Thus, the development of a simple and sensitive method to identify patients at high risk of AF would enable us to perform a 12-lead or Holter ECG recording with appropriate frequencies.

Patients at high risk of AF can be treated with renin-angiotensin system (RAS) inhibitors or statins, which lower blood pressure and are reported to reduce the onset of AF.[19–22] To date, several risk scores for AF have been developed.[23–25] However, although the previous scores achieve high area under the curve (AUC) values, they are complex and based on physical or ECG findings alone, and do not include laboratory or echocardiographic data. Moreover, these risk scores were developed using data obtained from the general population and mainly included individuals with white and black ancestry. Thus, the development of a simple and accurate score that includes objective assessment parameters, such as laboratory and echocardiographic data, is needed to more accurately assess AF risk in patients at high risk of AF. In addition, considering the fact that the number of patients with AF and HF has been dramatically increasing in Asia,[26–29] a useful model for risk prediction in Asian populations has been awaited.

In the present study, we thus examined the prevalence, characteristics and prognostic impact of AF in Stage A/B HF patients and aimed to develop a risk score for AF onset, using the database of our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study.[30–34]

Methods

The CHART-2 Study
The CHART-2 Study (n=10,219) is a multicenter, prospective observational study, as previously described (NCT00418041).[30–34] Patients aged ≥20 years with significant CAD or in Stage B/C/D HF, as defined according to the ACCF/AHA guidelines,[14] were consecutively enrolled from October 2006 to March 2010.[30–34] Clinical information was recorded at the time of enrollment and thereafter reviewed annually by trained clinical research coordinators. The CHART-2 Study was approved by the local ethics committees of each participating hospital and written informed consent was given by all patients.[30–34]

Study Design
The flowchart of the present study is shown in **Figure 1**. Among the 10,219 patients enrolled in the CHART-2 Study, 5,387 were identified in Stage A (CAD) or Stage B HF, and 5 were excluded for lack of ECG data. Among the 5,382 patients with Stage A/B HF, 1,217 (22.6%) had AF and 4,165 (77.4%) had no AF at enrollment. AF was diagnosed by cardiologists at each institute according to the clinical guidelines of the Japanese Circulation Society.[35] AF was defined as 'new AF' when documented for the first time in patients without AF at enrollment. We compared the clinical characteristics, therapies and long-term prognosis. Comparisons were made in terms of AF at enrollment, new-onset AF, type of AF (pAF vs. npAF), and combined factors for new-onset of AF and type of AF. The endpoints of the study included all-cause death, HF hospitalization, cardiovascular (CV) death and non-CV death. To examine the prognostic impact of new-onset AF, we compared the incidence of each endpoint between patients with AF at enrollment and those who developed AF without prior HF hospitalization. The patients were divided into 3 groups according to their risk score (low, intermediate, or high), and the prognosis of patients with new-onset AF was compared among the groups. In the present study, valvular heart disease (VHD) was defined as severe aortic and/or mitral valvular disease, which was diagnosed on echocardiography using standard criteria. Hypertension (HT) as an etiology was considered when a patient did not have ischemic heart disease (IHD), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) or VHD, but had a history of HT.

Statistical Analysis
All continuous variables are reported as mean±SD or median and interquartile range (IQR) and all categorical variables are reported as frequency (percentage). Welch's t-test and Fisher's exact test were used to compare the continuous and categorical variables, respectively. The Kaplan-Meier method and log-rank test were used to estimate survival curves and HF-free survival curves, respectively. Multivariable Cox proportional hazard models were used to assess the effect of AF on all-cause death and HF hospitalization. The covariates used in each multivariable analysis were selected using a stepwise method[36] from the following factors: sex, age, body mass index (BMI), systolic blood pressure (BP), diastolic BP, heart rate, history of HT, diabetes mellitus (DM), dyslipidemia, smoking, stroke and malignant disease, etiologies of CHF, including IHD, DCM, HCM, VHD and HT, left atrial dimension (LAd), end-diastolic left ventricular (LV) dimension (LVDd),

LV ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), mean corpuscular volume of red blood cells, hemoglobin, B-type natriuretic peptide (BNP), New York Heart Association (NYHA) class, and medical treatment, including β-blockers, calcium-channel blockers (CCB), RAS inhibitors, diuretics, statins, antiplatelet drugs, and warfarin. Among these covariates, sex, age, BMI, history of DM, stroke and malignant disease, LVDd, LVEF, eGFR, hemoglobin, NYHA class, CCB and antiplatelet drugs were selected for analysis of all-cause death.

Risk scores for the development of new-onset AF were developed based on the results of multivariable logistic regression model analysis. During this process, variables were selected using the following criteria: the use of drugs

and a history of HT, dyslipidemia, or DM were excluded in order to minimize the potential effects of drugs. Etiologies were also excluded because invasive procedures (e.g., catheter placement) were needed to define etiology. Continuous variables were converted into categorical variables using classification and regression trees (CART) to decide the most appropriate cutoff points.[37] In the CART analysis, each subgroup, lower or upper than the cutoff point, must have more than 208 in number to include at least 5% of patients without AF at enrollment, because subgroups with lower prevalence do not likely present the characteristics of patients with Stage B HF.

Finally, the following factors were used to develop risk scores for new-onset AF: sex, age ≥60 years, BMI ≥30 kg/m²,

Table 1. (A) Baseline Characteristics of Patients With AF at Enrollment, and (B) Baseline Characteristics of Patients With HF by Type of AF

A	All (n=5,382)	(−) AF (n=4,165)	(+) AF (n=1,217)	P value
Female, n, %	1,564 (29.1)	1,221 (29.3)	343 (28.2)	0.451
Age, years	67.6±12.0	66.8±12.3	70.5±10.4	<0.001
BMI, kg/m²	24.2±3.5	24.3±3.4	24.1±3.6	0.242
Etiology, n, %				
IHD	3,229 (60.0)	2,830 (67.9)	399 (32.8)	<0.001
DCM	135 (2.5)	80 (1.9)	55 (4.5)	<0.001
HCM	225 (4.2)	162 (3.9)	63 (5.2)	0.051
VHD	423 (7.9)	263 (6.3)	160 (13.1)	<0.001
HT	1,079 (20.0)	631 (15.2)	448 (36.8)	<0.001
Risk factors, n, %				
HT	4,652 (86.4)	3,589 (86.2)	1,063 (87.3)	0.318
DM	1,591 (29.6)	1,310 (31.5)	281 (23.1)	<0.001
Dyslipidemia	4,310 (80.1)	3,432 (82.4)	878 (72.1)	<0.001
Smoking	2,469 (48.5)	1,974 (50.1)	495 (43.0)	<0.001
Previous history, n, %				
MI	1,440 (26.8)	1,280 (30.7)	160 (13.1)	<0.001
Stroke	960 (17.8)	649 (15.6)	311 (25.6)	<0.001
Malignant disease	711 (13.2)	511 (12.3)	200 (16.4)	<0.001
Hemodynamics and LV function				
Systolic BP, mmHg	130.2±17.8	130.8±17.9	128.3±17.4	<0.001
Diastolic BP, mmHg	74.7±11.5	74.6±11.5	74.8±11.5	0.687
Heart rate, beats/min	69.7±13.2	69.1±12.5	72.0±15.0	<0.001
LVDd, mm	48.6±6.8	48.4±6.8	49.0±6.7	0.014
LAd, mm	39.5±7.5	37.8±6.1	45.1±8.9	<0.001
LVEF, %	64.9±11.5	65.2±11.6	63.6±10.9	<0.001
LVWT, mm	11.0±2.2	10.9±2.2	11.2±2.2	<0.001
Laboratory findings				
Hemoglobin, g/dL	13.6±1.7	13.6±1.7	13.7±1.8	0.098
eGFR, mL/min/1.73 m²	67.3±19.3	68.3±19.5	64.0±18.5	<0.001
Albumin, mg/dL	4.2±0.4	4.2±0.4	4.1±0.5	0.152
LDL-C, mg/dL	106.4±29.3	106.1±29.1	107.6±29.9	0.166
BNP, pg/mL	47.2 (20.8–113.0)	37.0 (18.1–81.3)	106.0 (51.8–195.2)	<0.001
Medications, n, %				
β-blockers	1,773 (32.9)	1,319 (31.7)	454 (37.3)	<0.001
RAS inhibitors	3,123 (58.0)	2,449 (58.8)	674 (55.4)	0.035
Diuretics	875 (16.3)	559 (13.4)	316 (26.0)	<0.001
Statins	2,389 (44.4)	2,057 (49.4)	332 (27.3)	<0.001
Digitalis	477 (8.9)	111 (2.7)	366 (30.1)	<0.001

(**Table 1** continued the next page.)

B	All (n=5,382)	(−) New AF (n=4,049)	(+) New AF (n=116)	P value	pAF (n=516)	cAF (n=701)	P value	P value (overall)
Female sex, n, %	1,564 (29.1)	1,186 (29.3)	35 (30.2)	0.836	160 (31.0)	183 (26.1)	0.062	0.244
Age, years	67.6±12.0	66.7±12.3	69.7±10.1	0.002	70.4±11.3	70.6±9.6	0.698	<0.001
BMI, kg/m²	24.2±3.5	24.3±3.4	24.6±3.6	0.250	23.9±3.4	24.3±3.8	0.085	0.524
Etiology, n, %								
IHD	3,229 (60.0)	2,763 (68.2)	67 (57.8)	0.020	213 (41.3)	186 (26.5)	<0.001	<0.001
DCM	135 (2.5)	79 (2.0)	1 (0.9)	0.727	5 (1.0)	50 (7.1)	<0.001	<0.001
HCM	225 (4.2)	152 (3.8)	10 (8.6)	0.014	34 (6.6)	29 (4.1)	0.066	0.004
VHD	423 (7.9)	252 (6.2)	11 (9.5)	0.171	52 (10.1)	108 (15.4)	0.008	<0.001
HT	1,079 (20.0)	607 (15.0)	24 (20.7)	0.113	168 (32.6)	280 (39.9)	0.010	<0.001
Risk factors, n, %								
HT	4,652 (86.4)	3,488 (86.1)	101 (87.1)	0.892	438 (84.9)	625 (89.2)	0.029	0.124
DM	1,591 (29.6)	1,279 (31.6)	31 (26.7)	0.310	111 (21.5)	170 (24.3)	0.271	<0.001
Dyslipidemia	4,310 (80.1)	3,338 (82.4)	94 (81.0)	0.710	396 (76.7)	482 (68.8)	0.002	<0.001
Smoking	2,469 (48.5)	1,916 (49.9)	58 (55.8)	0.274	209 (42.4)	286 (43.5)	0.719	<0.001
Previous history, n, %								
MI	1,440 (26.8)	1,250 (30.9)	30 (25.9)	0.263	80 (15.5)	80 (11.4)	0.040	<0.001
Stroke	960 (17.8)	631 (15.6)	18 (15.5)	1.000	109 (21.1)	202 (28.8)	0.003	<0.001
Malignant disease	711 (13.2)	485 (12.0)	26 (22.4)	0.002	82 (15.9)	118 (16.8)	0.696	<0.001
Hemodynamics and LV function								
Systolic BP, mmHg	130.2±17.8	130.8±17.9	130.3±18.2	0.757	129.7±17.9	127.3±16.9	0.023	<0.001
Diastolic BP, mmHg	74.7±11.5	74.7±11.5	71.9±10.9	0.007	74.5±11.2	75.0±11.8	0.511	0.849
Heart rate, beats/min	69.7±13.2	69.1±12.5	67.8±13.3	0.285	68.7±14.1	74.4±15.1	<0.001	<0.001
LVDd, mm	48.6±6.8	48.4±6.8	50.2±7.3	0.012	47.9±6.7	49.7±6.6	<0.001	<0.001
LAd, mm	39.5±7.5	37.7±6.1	41.7±6.8	<0.001	40.5±7.0	48.5±8.6	<0.001	<0.001
LVEF, %	64.9±11.5	65.3±11.6	63.1±12.4	0.070	66.0±10.5	61.9±10.9	<0.001	<0.001
LVWT, mm	11.0±2.2	10.9±2.2	11.6±2.6	0.011	11.2±2.3	11.2±2.1	0.911	<0.001
Laboratory findings								
Hemoglobin, g/dL	13.6±1.7	13.6±1.7	13.4±1.7	0.188	13.4±1.7	13.8±1.8	<0.001	0.018
eGFR, mL/min1.73m²	67.3±19.3	68.4±19.5	64.7±18.5	0.038	63.2±19.4	64.5±17.8	0.232	<0.001
Albumin, mg/dL	4.2±0.4	4.2±0.4	4.1±0.4	0.030	4.1±0.4	4.1±0.5	0.378	0.129
LDL-C, mg/dL	106.4±29.3	106.0±29.2	107.5±25.1	0.619	108.3±30.4	107.1±29.5	0.549	0.198
BNP, pg/mL	47.2 (20.8–113.0)	36.3 (17.7–79.0)	82.2 (33.9–190.6)	<0.001	70.1 (30.2–140.1)	139 (80.3–223.4)	<0.001	<0.001
Medications, n, %								
β-blockers	1,773 (32.9)	1,273 (31.4)	46 (39.7)	0.068	184 (35.7)	270 (38.5)	0.337	0.002
RAS inhibitors	3,123 (58.0)	2,377 (58.7)	72 (62.1)	0.504	278 (53.9)	396 (56.5)	0.382	0.105
Diuretics	875 (16.3)	533 (13.2)	26 (22.4)	0.008	84 (16.3)	232 (33.1)	<0.001	<0.001
Statins	2,389 (44.4)	2,007 (49.6)	50 (43.1)	0.187	155 (30.0)	177 (25.2)	0.068	<0.001
Digitalis	477 (8.9)	101 (2.5)	10 (8.6)	0.001	86 (16.7)	280 (39.9)	<0.001	<0.001

AF, atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; BMI, body mass index; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; HT, hypertension; IHD, ischemic heart disease; LAd, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVDd, end-diastolic left ventricular dimension; LVEF, left ventricular ejection fraction; LVWT, LV wall thickness; MI, myocardial infarction; NYHA, New York Heart Association; RAS, renin-angiotensin system; VHD, valvular heart disease.

pulse pressure ≥65mmHg, diastolic BP ≥70mmHg, heart rate ≥60 beats/min, history of stroke, smoking, eGFR ≤65mL/min/1.73m², BNP 70–175pg/mL, BNP ≥175pg/mL, aspartate aminotransferase (AST) ≥50IU/L or alanine aminotransferase (ALT) ≥50IU/L, uric acid ≥6mg/dL, LAd ≥45mm, LVDd ≥55mm, mean LV wall thickness (LVWT) ≥14mm and LVEF ≤45%. Next, a multivariable logistic regression model and a stepwise method were used to develop the risk scores for new-onset AF in the following 4 models. Model 1 included physical findings alone and present or past history: sex, age ≥60 years, BMI ≥30kg/m², pulse pressure ≥65mmHg, diastolic BP ≥70mmHg, heart rate ≥60 beats/min, and history of stroke and smoking.

Model 2 included all variables in model 1, and also included the following laboratory data: eGFR ≤65mL/min/1.73m², BNP 70–175pg/mL, BNP ≥175pg/mL, AST ≥50IU/L or ALT ≥50IU/L, HbA1c >7% and uric acid ≥6mg/dL. Model 3 included all variables in model 2, and also included the following echocardiographic data: LAd ≥45mm, LVDd ≥55mm, and mean LVWT ≥14mm and LVEF ≤45%. Model 4 included all the covariates that were significantly associated with onset of AF with P values <0.01 in the univariable logistic regression analysis: age ≥60 years, pulse pressure ≥65mmHg, heart rate ≥60 beats/min, eGFR 65mL/min/1.73m², BNP 70–175pg/mL, BNP ≥175pg/mL, LAd ≥45mm, LVDd ≥55mm, mean LVWT
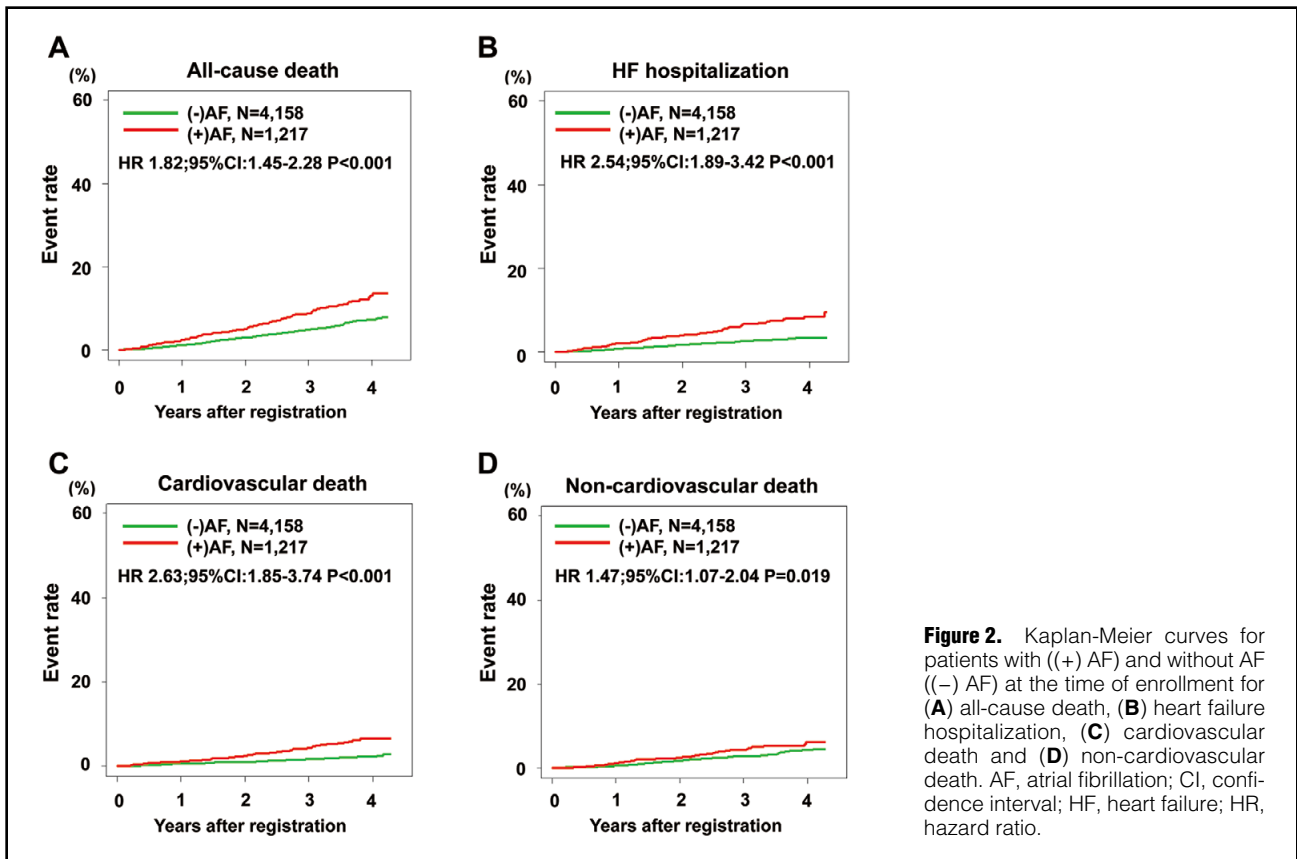
Figure 2. Kaplan-Meier curves for patients with ((+) AF) and without AF ((−) AF) at the time of enrollment for (**A**) all-cause death, (**B**) heart failure hospitalization, (**C**) cardiovascular death and (**D**) non-cardiovascular death. AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio.

≥14 mm and LVEF <45%. An integer score equivalent to the odds ratio (OR) of the particular risk factor was initially assigned to each risk factor selected in model 4. We then added and took back in turn the covariates from other models having score 1, in order to obtain the best set of the risk score. Finally, the score assigned to the components of the risk score was increased and decreased in turn, to determine the risk score with the largest AUC.

For the internal validation of our risk score, we performed a simulation study, which was formed with iteration of random partition of the data into training and validation sets.[38] First, we randomly divided the whole population data of 4,165 patients into 2,766 training (66.7%) and 1,389 validation (33.3%) sets, the latter being completely set aside during training. To train the model, the logistic regression model was applied to the training set with the covariates that were included in our AF risk score. Adjusted OR and respective scoring points for each covariate were determined by exactly the same method for the aforementioned full model described. The AF risk score obtained from the training data was applied to the samples in the validation set and the corresponding risk strata were predicted for each sample. This process was iterated 1,000 times and the median and IQR of the AUC of the receiver-operating characteristic curves were calculated. We also calculated the average incidence of new-onset of AF in each predicted risk stratum.

We also attempted to identify the best set of risk factors based on the covariates without echocardiographic data using the same protocol. The discriminatory power of the risk scores was estimated by the AUC. All statistical anal-ysis was performed using R software (version 3.2.1)[39] and P<0.05 was considered to be statistically significant.

Results

Baseline Patient Characteristics
The baseline characteristics of the patients with and without AF at enrollment are shown in **Table 1A**. Patients with AF at enrollment, as compared with those without it, were characterized by higher age, lower prevalence of DM, dyslipidemia and smoking, higher prevalence of prior stroke, lower eGFR, higher BNP, and a lower prevalence of IHD, but higher prevalence of DCM, HCM, VHD and HT. They were more frequently treated with β-blockers and diuretics and less frequently treated with statins. **Table 1B** shows the baseline characteristics of the patients with and without new AF, and those with pAF or npAF. The patients with new AF, as compared with those without it, were characterized by higher age, higher BNP level, lower eGFR and larger LAd. The patients with npAF, as compared with pAF patients, were characterized by a lower prevalence of IHD, lower LVEF, larger LAd and increased use of diuretics.

Prognostic Impact of AF
Among the 5,387 patients, 331 died and 180 were hospitalized for HF during the median follow-up period of 3.1 years. The cause of death was CV disease in 126, non-CV disease in 176 and unknown in 29. **Figure 2** shows the results of Kaplan-Meier estimates and univariable Cox proportional hazard models for all-cause death, HF hospi-
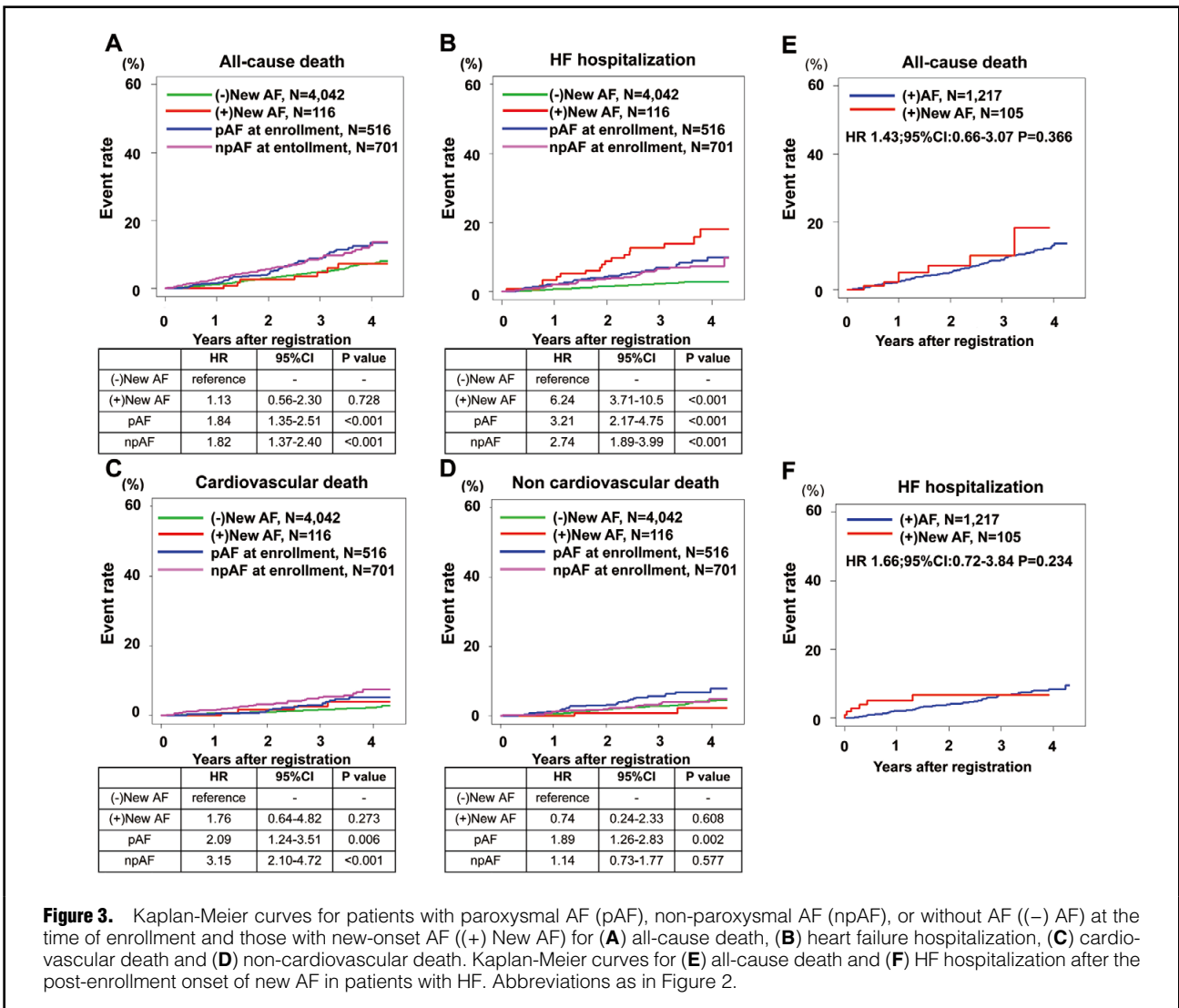
Figure 3. Kaplan-Meier curves for patients with paroxysmal AF (pAF), non-paroxysmal AF (npAF), or without AF ((−) AF) at the time of enrollment and those with new-onset AF ((+) New AF) for (**A**) all-cause death, (**B**) heart failure hospitalization, (**C**) cardiovascular death and (**D**) non-cardiovascular death. Kaplan-Meier curves for (**E**) all-cause death and (**F**) HF hospitalization after the post-enrollment onset of new AF in patients with HF. Abbreviations as in Figure 2.

talization, CV death and non-CV death. AF at enrollment was significantly associated with an increased incidence of each event.

Among the 4,165 patients without AF at enrollment, 116 (2.8%) newly developed AF during the follow-up period. As compared with patients without new-onset AF (n=4,042), this group had an increased risk of HF hospitalization (**Figure 3B**), but not for all-cause death (**Figure 3A**), CV death (**Figure 3C**), or non-CV death (**Figure 3D**). Both the patients with pAF and those with npAF had increased mortality rates and risk of HF hospitalization (**Figure 3A–D**).

Multivariable Cox proportional hazard models showed that AF at enrollment was significantly associated with increased all-cause death and HF hospitalization, even after adjustment for clinical variables (**Figure 4A**), whereas new-onset AF was only associated with increased HF hospitalization (**Figure 4B**). Among AF patients, only pAF was associated with increased HF hospitalization (**Figure 4B**). The prognosis of patients with new-onset AF, as observed from the time of onset, was comparable with that of patients with AF at the time enrollment (**Figure 3E,3F**).

Notably, no significant interaction was noted between the prognostic impact of new AF and sex (**Table S1**).

Factors Associated With AF and Development of Risk Score

Among the patients without AF at enrollment, 116 developed AF during the follow-up period. The factors related to new-onset AF are shown in **Table 2**. The addition of smoking and pulse pressure as covariates to model 4 increased the AUC. The risk factors and highest scores assigned for each factor with the largest AUC (0.76) are shown in **Table 3**. The obtained AUC value was similar between male and female patients (0.76 and 0.77, respectively), and was also similar and high enough between patients with and without IHD (0.79 and 0.72, respectively). The incident rate of new-onset AF clearly increased as the sum of the risk score increased (**Figure 5A**).

Based on the total risk score, the patients were stratified into 3 risk groups for new-onset AF; low risk (score 0–3, n=1,919), intermediate risk (score 4–8, n=927), and high risk (score 9–13, n=89) (**Figure 5A**). The intermediate- and high-risk groups were significantly associated with an
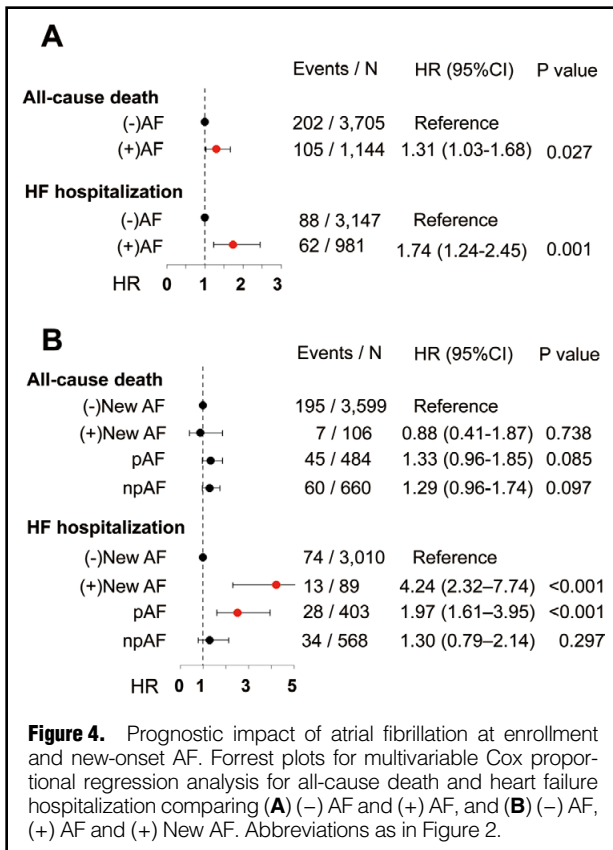
Figure 4. Prognostic impact of atrial fibrillation at enrollment and new-onset AF. Forrest plots for multivariable Cox proportional regression analysis for all-cause death and heart failure hospitalization comparing (**A**) (−) AF and (+) AF, and (**B**) (−) AF, (+) AF and (+) New AF. Abbreviations as in Figure 2.

Table 2. Factors Related to New-Onset AF

Factor	Odds ratio	P value
(A) Model 1		
Age ≥60 years	2.479	0.004
Smoking	1.438	0.076
Pulse pressure ≥60 mmHg	1.557	0.039
Heart rate ≥60 beats/min	0.713	0.127
(B) Model 2		
Smoking	1.454	0.128
eGFR ≤65 mL/min/1.73 m²	2.399	0.001
BNP 70–175 pg/mL	2.248	0.006
BNP ≥175 pg/mL	4.591	<0.001
(C) Model 3		
Smoking	1.706	0.043
eGFR ≤65 mL/min/1.73 m²	2.199	0.004
BNP 70–175 pg/mL	1.791	0.060
BNP ≥175 pg/mL	2.832	0.001
LAd ≥45 mm	3.347	<0.001
LVDd ≥55 mm	1.605	0.099
(D) Model 4		
Age ≥60 years	1.908	0.037
BNP 70–175 pg/mL	1.543	0.112
BNP ≥175 pg/mL	3.022	<0.001
LAd ≥45 mm	2.804	<0.001
LVDd ≥55 mm	1.793	0.019
LVWT ≥14 mm	1.786	0.046

LV, left ventricle. Other abbreviations as in Table 1.

Table 3. Values Assigned to the Risk Factors of New-Onset AF

Risk factor	Score
Age ≥60 years	1
Smoking	1
Pulse pressure ≥65 mmHg	1
eGFR ≤65 mL/min/1.73 m²	1
BNP 70–175 pg/mL	1
BNP ≥175 pg/mL	3
LAd ≥45 mm	3
LVDd ≥55 mm	2
LVWT ≥14 mm	1

Abbreviations as in Tables 1,2.

increased incidence of new-onset AF compared with the low-risk group (hazard ratio [HR]: 5.2, 95% confidence interval [CI]: 3.08–8.72, P<0.001 for the intermediate-risk group and HR: 15.2, 95% CI: 7.66–30.0, P<0.001 for the high-risk group) (**Figure 5B**). The results of the same evaluation performed without echocardiographic data are shown in **Figure S1**. Using this analytical approach, the AUC value was 0.72, which was lower than the score obtained using the model that included echocardiographic data (AUC 0.76), and the incident rate of new-onset AF increased as the sum of the risk score increased (**Figure S1**). Notably, the value assigned to eGFR as a covariate increased from 1 to 2 (**Table S2**).

For internal validation of the accuracy of our risk score, we performed a simulation study with 1,000 runs of iteration. The median AUC of our score in the validation set was 0.71 (training AUC: median=0.76, IQR=0.03; validation AUC: median=0.71, IQR=0.061).

Discussion

The major findings of the present study were: (1) 22.6% of patients with Stage A/B HF had AF at enrollment; (2) of the 4,165 patients without AF at enrollment, 116 newly developed AF during the median 3.1-year follow-up period; (3) AF at enrollment was associated with increased incidence of both all-cause death and HF hospitalization, whereas new AF was associated with HF hospitalization but not with all-cause death; and (4) the risk score developed based on the results of multivariable analysis was able to stratify the risk of AF development with reasonable accuracy in Stage A/B HF patients.

Prevalence, Patients' Characteristics and Related Factors of AF

In the present study of Stage A/B HF patients in the CHART-2 Study, the prevalence of AF was 22.6% at enrollment. Although this rate is lower than previously reported in CHF patients,[11–13] it is markedly higher than that of the general population (1.0–2.1%), even considering the higher median age of the present cohort.[1–4] Consistent with previous reports,[5,7,15,40] the patients with AF were characterized by higher age but lower prevalence of DM and IHD.

In the present study, the factors related to the risk of new-onset AF included higher age, smoking, pulse pressure, eGFR, BNP, LAd, LVDd, and LVWT. Of these, higher age,[41] smoking,[41] pulse pressure,[42] eGFR[43] and
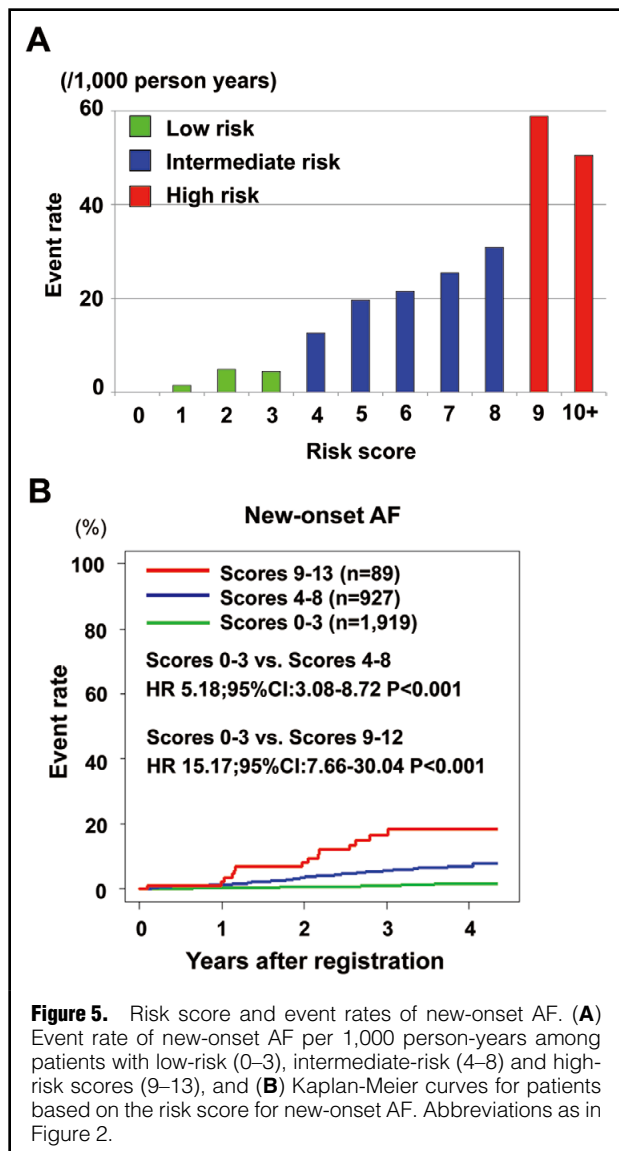
Figure 5. Risk score and event rates of new-onset AF. (**A**) Event rate of new-onset AF per 1,000 person-years among patients with low-risk (0–3), intermediate-risk (4–8) and high-risk scores (9–13), and (**B**) Kaplan-Meier curves for patients based on the risk score for new-onset AF. Abbreviations as in Figure 2.

factors, a finding consistent with previous reports in the general population and in patients with aortic valve stenosis or CAD.[5–7,15,40] On the other hand, new-onset AF was associated with an increased incidence of HF hospitalization, but not with all-cause death in the present study. These findings suggest that, in patients in Stage A/B, the prognostic impact of AF on all-cause death may become more evident later than that on HF development. Interestingly, in patients with Stage C/D HF, we recently reported that new-onset AF without prior HF worsening was associated with poor prognosis, whereas no such association was noted for new-onset AF after hospitalization for worsening HF.[11] Thus, the long-term follow-up of the CHART-2 cohort could provide further insight into the effect of new-onset AF on patients with Stage A/B HF, especially in relation to HF development.

Risk Score for New-Onset AF
In the present study, we developed a simple and reliable risk score for AF onset. Notably, our risk score had good discrimination ability, with an AUC 0.76, which is comparable to previous risk scores.[23–25] Because our score included both laboratory and objective echocardiographic data, it may outweigh physical findings, such as the intensity of murmurs. Compared with previous scores,[23,24] our risk score comprises fewer variables with a simple integer score ranging from 1 to 3. The use of such a simple and objective score may allow easy discrimination of patients at high risk for AF, thereby enabling early diagnosis and treatment, or even prevention of AF. However, removing the echocardiographic data (e.g., LVH and LA and LV dilatation) from our full risk score, reduced the AUC, indicating the importance of these factors in reflecting the pressure and volume load of the heart.[46,47]

Benefit of Prevention, Early Diagnosis and Treatment of AF
The present risk score enabled identification of patients at high risk for HF and future development of AF. Because AF is often asymptomatic[18,48–50] and is associated with similar risk of stroke regardless of its type (symptomatic vs. asymptomatic or paroxysmal vs. non-paroxysmal),[17,51] a simple risk score to identify patients at high risk of AF may be clinically important to improve their prognosis. In other words, identification of patients at high risk for AF development may help to prevent AF, resulting in a decrease in HF exacerbation, because new-onset AF was associated with increased incidence of admission for HF in the present study. Although continuous monitoring is effective for detecting new-onset AF,[48,52] such an approach may not be feasible for all patients with Stage A/B HF from a cost-effectiveness viewpoint.

Study Limitations
Several limitations of the present study should be mentioned. First, the mean age of the patients was relatively high and all patients were Japanese. Considering the possible effect of racial differences,[22] this might limit the application of our risk score to other cohorts. Second, we had insufficient ECG data other than cardiac rhythm, with which the accuracy of the risk score could have been improved. Third, inclusion of the echocardiographic data may limit the application of the present risk score in the general population. Finally, although we performed an internal validation analysis and confirmed the reproducibility and accuracy of our score, external validation was

BNP[44] were also previously found to be major factors for AF. Interestingly, the stepwise selection in the multivariable Cox proportional hazard models in the present study included pulse pressure, but not HT, because pulse pressure, a surrogate measure for aortic stiffness,[45] may more accurately reflect the effect of long-term pressure load than systolic BP. Otherwise, a higher use of RAS inhibitors may have reduced the effect of systolic BP or history of HT on the onset of AF in the Stage A/B patients in the present study. LAd, LVDd, and LVWT on echocardiography, reflecting LV volume and pressure load,[46,47] were also factors related to new-onset AF in the present study. As LA and LV remodeling on ECG were previously found to be related to new-onset AF,[24] the corresponding values determined from echocardiography analysis in the present study may be related to new-onset AF.

Prognostic Impact of AF
In the present study, AF at enrollment was associated with poor prognosis for both all-cause death and HF hospitalization even after adjustment for possible confounding

not performed. Thus, our results remain to be confirmed in other cohorts and populations.

Conclusions

In the present study, we demonstrated that AF was associated with worse prognosis in patients at high risk of HF. We also developed a simple and accurate risk score to identify patients at high risk for AF onset. Further studies are needed to confirm our findings and to validate the risk score in other populations.

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Supplementary Files

Supplementary File 1

Figure S1.   Risk score without echocardiography data and event rates of new-onset AF.

Table S1.   Prognostic impact of new-onset AF by sex

Table S2.   Values assigned to the risk factors of new-onset AF without echocardiographic data

CHART-2 Study Investigators

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-16-0759