A Cluster Analysis of the Japanese Multicenter Outpatient Registry of Patients With Atrial Fibrillation

Taku Inohara, MD, PhD[a,b], Jonathan P. Piccini, MD, MHS[b], Kenneth W. Mahaffey, MD[c], Takehiro Kimura, MD, PhD[a], Yoshinori Katsumata, MD, PhD[a], Kojiro Tanimoto, MD, PhD[d], Kohei Inagawa, MD, PhD[d], Nobuhiro Ikemura, MD[a], Ikuko Ueda, PhD[a], Keiichi Fukuda, MD, PhD[a], Seiji Takatsuki, MD, PhD[a], and Shun Kohsaka, MD[a,*]

Recently, cluster analysis was used to identify unique clinically relevant phenotypes of atrial fibrillation (AF) in a cohort from the United States (US) and classified clusters according to the presence of comorbid behavioral disorders, those with conduction disorders, or atherosclerotic comorbidities. Whether these phenotypes are consistent in AF cohorts outside the US remains unknown. Thus, we sought to conduct a cluster analysis in a cohort of Japanese AF patients. We conducted a cluster analysis of phenotypic data (46 variables) in an AF patient cohort recruited from 11 Japanese sites participating in the KiCS-AF Registry. Overall, 2,458 AF patients (median [IQR] age, 68.0 [60.0 to 76.0]; 30.3% female; median [IQR] CHA_2DS_2-Vasc, 2 [1, 3]) were analyzed. Similar to the US cohort, atherosclerotic comorbidities were identified as distinguishing factors to characterize clusters. Distribution of AF type and left atrial (LA) size substantially varied and was the key feature for cluster formation. CHA_2DS_2-Vasc score also contributed to cluster formation, although behavioral disorders and/or conduction disorders did not readily characterize clusters. Subsequently, the cohort was classified into 3 clusters: (1) Younger paroxysmal AF (n = 1,190); (2) Persistent/permanent AF with LA enlargement (n = 1,143); and (3) Atherosclerotic comorbid AF in elderly patients (N = 125). In conclusion, conventional classifications, such as atherosclerotic risk factors and CHA_2DS_2-Vasc score contributed to cluster formation in mutually, whereas in nonatherosclerotic clusters, AF type or LA size rather than the presence or absence of behavior risk factors or sinus node dysfunction (tachy-brady syndrome) seemed to contribute to cluster formation in the Japanese cohort. **(Am J Cardiol 2019;124:871−878)**

Classification of atrial fibrillation (AF) is usually dependent on the duration and type of AF, atrial size, and risk of thromboembolism.[1] However, given the heterogeneity, these conventional classifications may not be sufficient to characterize patients with AF. Recently, a cluster analysis, an unsupervised data-driven approach, was applied to several cardiovascular disease states and was able to improve disease phenotype classification.[2-6] In the field of AF, this classification and analytic technique was used in a US-based AF cohort and identified 4 unique clinically relevant phenotypes: (1) patients with considerably lower rates of risk factors and comorbidities than all other clusters; (2) younger patients characterized by high prevalence of liver disease, alcohol abuse, drug abuse, and current smoking; (3) older patients with high prevalence of device implantation owing to the sinus node dysfunction; and (4) patients with high prevalence of coronary artery disease.[7] Importantly, conventional AF classifications did not drive cluster formation, and these distinct clusters were associated with different risks for cardiovascular outcomes. However, it is not known whether these phenotypes are consistent in AF cohorts outside the US. Therefore, we sought (1) to conduct a cluster analysis in Japanese AF patients, (2) to identify clusters of AF patients who share similar phenotypes, (3) to compare the identified clusters from the Japanese cohort with those from the US-based cohort, and (4) to assess the association between identified clusters and cardiovascular outcomes.

Methods

The cohort of this analysis was derived from the Keio Interhospital Cardiovascular Studies for AF (KiCS-AF) registry.[8] The KiCS-AF Registry is a clinician-initiated, prospective, multicenter outpatient AF registry that enrolls patients from the metropolitan Tokyo area. KiCS-AF was designed to collect clinical variables and outcome measures for AF patients. Dedicated clinical research coordinators are assigned to each hospital, and data on approximately 150 variables are collected for each patient. The KiCS-AF

[a]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan; [b]Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; [c]Department of Medicine, Stanford University, Stanford, California; and [d]Department of Cardiology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan. Manuscript received April 2, 2019; revised manuscript received and accepted May 31, 2019.

Funding: This study was funded Grant-in-Aid from Scientific Research from the Japan Agency for Medical Research and Development (Pooled analysis for identifying RISK factors for Atrial Fibrillation and cardioembolic stroke in Japanese: ID. 924988) and the Japan Society for the Promotion of Science (Grant No. 16H05215 and 16KK0186) and by an unrestricted research grant from Bayer Yakuhin Ltd.

See page 877 for disclosure information.

*Corresponding author: Tel: +81 3 5843 6702; fax: +81 3 5363 3875.
E-mail address: sk@keio.jp (S. Kohsaka).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.05.071

registry ensures data traceability by tracking the staff who approved the data and data-entry personnel at the participating institutions. It also validates data consistency via inspections of the participating institutions. Additionally, the database administrators provide on- and off-site training systems to guide the clinical research coordinators on how to input data consistently.

In addition to the traditional data collected by health care providers, KiCS-AF also collected patient reported outcomes. Participants completed a validated AF-related quality-of-life instrument called the Atrial Fibrillation Effects on Quality of Life questionnaire (AFEQT; http://www.afeqt.org). The AFEQT is a 20-item survey using 7-point response scales, which measures AF-specific health status and ranges from 0 to 100, with 100 representing the best possible health status and 0 representing the worst.[9] To recruit treatment-naive patients, only patients with a diagnosis of AF within 6 months before the initial visit were enrolled. We limited the enrollment of AF patients to those who had a new diagnostic coding for AF within the previous 6 months. Data regarding the patients' background, symptoms, previous and current drug use (including oral anticoagulants [OACs]), electrocardiography and echocardiography results, and blood sampling test results were collected from the medical records.

We included all patients from the KiCS-AF registry enrolled in September 2012 and June 2017 in the cluster analysis of the baseline data. For the purpose of the analysis evaluating the association between identified clusters and clinical outcomes at 1 year, we excluded the patients who had not met the term for a 1-year follow-up visit. Follow-up survey was conducted by a hospital chart review, or by contacting patients or referring physicians via mail or telephone on an annual basis. The outcome of interest was major adverse cardiovascular or neurological events (MACNE), which was defined as a composite of all-cause death, myocardial infarction, and stroke. The institutional review board at each participating hospital approved the study's protocol, and all participants provided written informed consent. Before the launch of the KiCS-AF registry, information regarding the objectives of the study and its social significance was provided to the University Hospital Medical Information Network, which recognized KiCS-AF as an acceptable registry for clinical study registration (UMIN 000022229).

In this analysis, hierarchical clustering with complete linkage method was performed.[10] For calculating the distance between observations or clusters, the Gower's distance was used, given the mixed data types of binary, ordinary, and continuous variables.[10] The distance was calculated on the basis of 46 variables including demographics (age, sex, body mass index), vital signs (heart rate, diastolic, and systolic blood pressure), laboratory data (estimated glomerular filtration rate, hematocrit), medical history (smoking, cancer, hypertension, diabetes, hyperthyroidism and hypothyroidism, gastrointestinal bleeding, obstructive sleep apnea, dialysis, dyslipidemia, liver function [MELD score calculated from serum creatinine, bilirubin, international normalized ratio, and sodium], chronic obstructive lung disease, drug abuse), cardiovascular history (family history of AF, peripheral vascular disease, sinus node dysfunction, stroke or transient ischemic attack, heart failure, moderate or severe mitral stenosis, previous valve surgery, device implantation, coronary artery disease, myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, drug-eluting stent implantation, cardioversion, antiarrhythmic drug use, catheter ablation, atrioventricular node ablation), electrocardiographic finding (sinus rhythm, interventricular conduction abnormality, left ventricular hypertrophy), echocardiographic finding (left ventricular ejection fraction, left atrial [LA] size), type of AF (first detected or new-onset vs paroxysmal vs persistent vs permanent), and baseline quality-of-life scale measured by AFEQT. The selection of these variables was in accordance with a previous study.[7] The goal was to determine clusters that were homogeneous and that illustrated particular types of patients, without knowing the outcomes. According to the tree diagram (Figure 1), the groupings from 3 clusters or 6 clusters could be considered. To ensure the adequate number of patients in each cluster, 3 clusters were employed in this study.

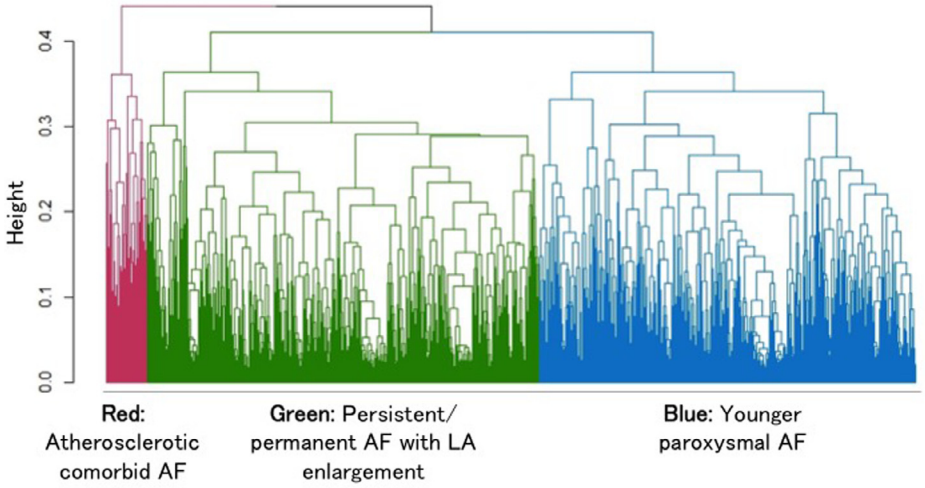

Figure 1. Tree diagram describing the clustering process

Each branch represents each patient. The Y axis indicates height, which is a measure of the homogeneity of merged patients or clusters. Small values of the height indicate that the merged clusters were similar, and large values indicate the combination of two dissimilar (heterogeneous) clusters.

Abbreviation: AF = atrial fibrillation.

We reported the medians with interquartile ranges or means with standard deviations for continuous variables and counts with percentages for categorical variables. The Kruskal-Wallis test and the chi-squared test were used to compare the baseline differences among clusters. Cox hazard regression models were used to adjust for the differences in baseline characteristics among clusters. These analyses were adjusted for each component of CHA_2DS_2-Vasc including age, sex, heart failure, hypertension, stroke or transient ischemic attack, peripheral vascular disease, and diabetes.

All variables had <5% of missingness, except for MELD score (28.0%), diastolic blood pressure (22.5%), left ventricular ejection fraction (17.7%), LA size (15.3%), mitral stenosis (14.0%), and estimated glomerular filtration rate (5.8%). Multiple imputation was used for missing values using the "mice" package in R. All statistical analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). All p-values are 2-sided, and $p < 0.05$ was considered statistically significant. The 95% confidence interval was reported.

Results

Table 1 compares the baseline demographics and characteristics between the KiCS-AF registry (Japanese dataset) and ORBIT-AF registry (US dataset).[7] Compared with those registered in the ORBIT-AF registry, patients in the KiCS-AF registry were more likely to be male and younger, and were treated with rhythm control and anticoagulation. Importantly, patients in the KiCS-AF registry had less comorbidities and lower CHA_2DS_2-VASc scores than did those in the ORBIT-AF registry. We applied a cluster analysis to a total of 2,458 AF patients (median [IQR] age, 68.0 [60.0 to 76.0]; 30.3% female; median [IQR] CHA_2DS_2-Vasc, 2 [1, 3]) from 11 sites and identified 3 clusters (Figure 1, Table 2).

Patients in the younger paroxysmal AF cluster (n = 1,190) were the youngest (mean [SD] age, 65.9 [11.7] years) and the most likely to be male (67.8%). The prevalence of comorbidities was relatively low. The unique characteristic of these patients is that almost all of them had paroxysmal AF (96.5%). More than half of the patients in this cluster were symptomatic and treated with a rhythm control strategy.

Similar to the younger paroxysmal AF cluster, the 1,143 patients in the persistent/permanent AF with LA enlargement cluster had a lower prevalence of comorbidities compared with the atherosclerotic comorbid AF cluster. The key and distinguishing characteristics of this cluster were the highest rate of persistent/permanent AF and the greatest dilated LA (mean [SD] LA diameter, 4.4 [0.7] cm). Importantly, more than half of the patients in this cluster were asymptomatic and more than one-third had their AF detected during a routine health check-up.

The patients in the atherosclerotic comorbid cluster were the oldest (mean [SD] age, 73.4 [8.3] years) and the most likely to be female (76.0%). A major feature of patients in this cluster is that most patients (89.6%) had a history of coronary artery disease and had high prevalence of previous myocardial infarction (61.6%) and percutaneous coronary intervention (87.2%). In addition, they had high rates of atherosclerotic comorbidities such as hypertension, dyslipidemia, and diabetes.

We examined the relationship between the identified clusters and conventional AF classifications (Figure 2). The distribution of AF type quite varied among the clusters and was the key feature to characterize clusters. Similarly, LA size was quite different among the clusters, and its enlargement characterized the persistent/permanent AF with LA enlargement cluster. CHA_2DS_2-Vasc score was not different in a clinically meaningful way between younger paroxysmal AF and low-comorbidity paroxysmal AF clusters, but considering the advanced age and presence of comorbidity, CHA_2DS_2-Vasc score was significantly higher in the atherosclerotic comorbid AF cluster than in the other 2 clusters.

After excluding patients who had not met the term for a 1-year follow-up visit (n = 805), the relationship between the identified clusters and cardiovascular outcomes was evaluated in 1,653 patients. A total of 63 MACNE (3.8%) occurred at the 1-year follow-up, and their occurrence varied significantly among clusters (Figure 3; $p = 0.002$ by log-rank test). However, after the adjustment for components of CHA_2DS_2-VASc, there was no statistically significant difference among clusters (persistent/permanent AF with LA enlargement vs low-comorbidity paroxysmal AF: adjusted hazard ratio [aHR] 1.45, 95%CI 0.82 to 2.58, $p = 0.20$; atherosclerotic comorbid AF vs low-comorbidity paroxysmal AF: aHR 1.47, 95%CI 0.61 to 3.56, $p = 0.39$).

Discussion

We conducted a cluster analysis of Japanese outpatients with AF and identified 3 phenotype clusters. Conventional classifications, such as type of AF, LA size, and CHA_2DS_2-VASc score, contributed to the formation of these clusters. In contrast to cluster phenotypes described in the US cohort, the presence or absence of behavior risk factors or sinus node dysfunction (tachy-brady syndrome) did not contribute to cluster formation. The difference in the identified clusters between these cohorts emphasizes the heterogeneity observed among AF patients as well as regional differences between registries.

There are some important similarities between the cluster phenotypes characterized by the KiCS-AF and ORBIT AF cohorts. The atherosclerotic comorbid AF cluster phenotype was consistently observed in both cohorts.[7] Considering the highest CHA_2DS_2-VASc score, the rate of MACNE was the highest among this cluster in both cohorts, although it did not reach statistical significance after the adjustment in our dataset, which was likely due to the limited power subsequent to the small sample size. The other important distinguishing feature in this cluster was the high prescription rates of antiplatelet agent, statin, renin-angiotensin inhibitors, and beta-blockers. Given the recent emphasis on treatment of AF risk factors, this observation is important. As this cluster phenotype appears preserved across cohorts, identification of interventions specific to these patients is an important goal for future research.

The type of AF and LA size served as the main drivers to characterize clusters in our dataset, but they did not contribute significantly to cluster phenotype formation in the US-based cohort.[7] A widely available primary care and screening

Table 1
Comparison of baseline characteristics between Japanese dataset and US dataset

Variables	KiCS-AF (N = 2458)	ORBIT-AF (N = 9749)
Demographics and vital signs		
Men	1713 (69.7%)	5599 (57.4%)
Age, mean ± SD, (years)	67.4 ± 11.7	73.6 ± 10.9
BMI, mean ± SD, (Kg/m^2)	23.6 ± 3.8	30.5 ± 7.7
SBP, mean ± SD, (mmHg)	128.7 ± 18.2	126.4 ± 16.8
DBP, mean ± SD, (mmHg)	76.2 ± 13.2	73.0 ± 10.6
HR, mean ± SD, (bpm)	78.2 ± 17.6	71.9 ± 13.0
Sinus rhythm	1164 (48.0%)	3284 (33.7%)
Risk score		
CHA_2DS_2-VASc, mean (SD)	2.39 ± 1.70	3.94 ± 1.77
Symptom		
Asymptomatic	1026 (41.7%)	3726 (38.2%)
Comorbidity		
Heart failure	414 (16.9%)	3204 (32.9%)
Sick sinus syndrome	82 (3.4%)	1722 (17.7%)
Device implantation	51 (2.1%)	2690 (27.6%)
Coronary artery disease	196 (8.0%)	3535 (36.3%)
Prior myocardial infarction	95 (3.9%)	1562 (16.0%)
Percutaneous coronary intervention,	122 (5.0%)	1689 (17.3%)
Coronary artery bypass grafting	21 (0.9%)	1442 (14.8%)
Hypertension	1364 (55.8%)	8103 (83.1%)
Dyslipidemia	809 (33.1%)	7042 (72.2%)
Diabetes	400 (16.4%)	2874 (29.5%)
Stroke or transient ischemic attack	210 (8.6%)	1479 (15.2%)
Intracranial hemorrhage	35 (1.4%)	75 (0.8%)
Gastrointestinal bleeding	34 (1.4%)	893 (9.2%)
Peripheral artery disease	81 (3.3%)	1309 (13.4%)
Chronic obstructive lung disease	60 (2.5%)	1605 (16.5%)
Estimated glomerular filtration rate, mean ±SD, ($mL/min/1.73\ m^2$)	62.6 ± 17.0	68.3 ± 23.3
Obstructive sleep apnea syndrome	73 (3.0%)	1783 (18.3%)
Dialysis	16 (0.7%)	124 (1.3%)
Current smoker	406 (16.6%)	556 (11.8%)
Drug abuse	2 (0.1%)	127 (1.3%)
Alcohol abuse	23 (0.9%)	380 (3.9%)
Echocardiography		
Left ventricular ejection fraction, mean ± SD	57.6 ± 8.2	54.6 ± 12.2
Left atrial diameter, mean ± SD	4.1 ± 0.8	4.5 ± 0.9
Atrial fibrillation type		
Initial/new-onset	145 (6.0%)	438 (4.5%)
Paroxysmal	1212 (49.8%)	4940 (50.7%)
Persistent	664 (27.3%)	1635 (16.8%)
Permanent	373 (15.3%)	2736 (28.1%)
Unknown	41 (1.7%)	NA
Antiplatelet therapy		
Aspirin	230 (9.4%)	4318 (44.3%)
Clopidogrel	85 (3.5%)	692 (7.1%)
Anticoagulation therapy		
Any anticoagulation	2016 (82.5%)	7445 (76.4%)
Any anticoagulation in CHA_2DS_2-VASc ≥2	1435 (89.1%)	6942 (78.2%)
Treatment		
Rhythm control	1318 (54.0%)	3083 (31.6%)
Prior catheter ablation	160 (6.5%)	450 (10.1%)
Prior surgical maze	7 (0.3%)	189 (1.9%)
Prior atrioventricular node ablation	16 (0.7%)	218 (2.2%≥)

Abbreviations: KiCS-AF = Keio Interhospital Cardiovascular Studies for AF; ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DPB = diastolic blood pressure; HR = heart rate.
Characteristics in the ORBIT-AF Registry are derived from reference 7.

network in Japan may explain this discrepancy. In Japan, screening electrocardiograms are performed as part of the worksite annual health check-up and are recommended for individuals with a high-risk profile in community-based medical examinations.[11,12] In our dataset, 26.0% of AF cases were detected at routine heath check-ups. Patients with

Table 2
Patient characteristics stratified by identified clusters

Variables	Younger paroxysmal AF (N = 1190)	Persistent/permanent AF with LA enlargement (N = 1143)	Atherosclerotic comorbid AF (N = 125)	p
Demographics and vital signs				
Men	807 (67.8%)	811 (71.0%)	95 (76.0%)	0.074
Age, mean ± SD, (years)	65.91 ± 11.73	68.24 ± 11.76	73.36 ± 8.28	<0.001
BMI, mean ± SD, (Kg/m^2)	23.30 ± 3.60	23.85 ± 4.02	23.85 ± 3.56	0.002
SBP, mean ± SD, (mmHg)	131.14 ± 17.90	126.73 ± 18.30	124.68 ± 16.81	<0.001
DBP, mean ± SD, (mmHg)	75.63 ± 12.25	77.35 ± 13.84	72.33 ± 13.78	<0.001
HR, mean ± SD, (bpm)	73.92 ± 16.12	83.3 ± 17.74	71.77 ± 17.12	<0.001
Sinus rhythm	932 (79.1%)	166 (14.8%)	66 (53.2%)	
Risk score				
CHA_2DS_2-VASc, mean ± SD	2.16 ± 1.65	2.44 ± 1.64	4.05 ± 1.66	<0.001
CHA_2DS_2-VASc description	614 (51.7%)	574 (50.7%)	46 (36.8%)	0.006
Symptom & health check-up				
Palpitation	670 (56.3%)	308 (26.9%)	38 (30.4%)	<0.001
Dyspnea	135 (11.3%)	250 (21.9%)	18 (14.4%)	<0.001
Difficult activity	44 (3.7%)	31 (2.7%)	3 (2.4%)	0.35
Dizziness	66 (5.5%)	39 (3.4%)	4 (3.2%)	0.034
Fatigue	40 (3.4%)	57 (5.0%)	2 (1.6%)	0.05
Chest pain	43 (3.6%)	24 (2.1%)	5 (4.0%)	0.073
Syncope	32 (2.7%)	7 (0.6%)	2 (1.6%)	<0.001
No symptom	367 (30.8%)	589 (51.5%)	70 (56.0%)	<0.001
Health check-up	233 (19.6%)	397 (34.7%)	9 (7.2%)	<0.001
Comorbidity				
Heart failure	96 (8.1%)	279 (24.6%)	39 (31.2%)	<0.001
Sick sinus syndrome	64 (5.4%)	14 (1.2%)	4 (3.2%)	<0.001
Device implantation	33 (2.8%)	14 (1.2%)	4 (3.2%)	0.11
Coronary artery disease	49 (4.1%)	35 (3.1%)	112 (89.6%)	<0.001
Prior myocardial infarction	13 (1.1%)	5 (0.4%)	77 (61.6%)	<0.001
Percutaneous coronary intervention	11 (0.9%)	2 (0.2%)	109 (87.2%)	<0.001
Coronary artery bypass grafting	6 (0.5%)	3 (0.3%)	12 (9.6%)	<0.001
Hypertension	634 (53.4%)	638 (56.3%)	92 (73.6%)	<0.001
Dyslipidemia	393 (33.1%)	326 (28.8%)	90 (72.0%)	<0.001
Diabetes	174 (14.7%)	185 (16.3%)	41 (32.8%)	<0.001
Stroke or transient ischemic attack	112 (9.4%)	83 (7.3%)	15 (12.0%)	0.073
Intracranial hemorrhage	17 (1.4%)	16 (1.4%)	2 (1.6%)	0.986
Gastrointestinal bleeding	14 (1.2%)	13 (1.1%)	7 (5.6%)	<0.001
Peripheral artery disease	28 (2.4%)	34 (3.0%)	19 (15.2%)	<0.001
Chronic obstructive lung disease	22 (1.9%)	32 (2.8%)	6 (4.8%)	0.071
Estimated glomerular filtration rate, mean ± SD, ($mL/min/1.73m^2$)	64.83 ± 16.85	61.19 ± 16.84	54.00 ± 15.85	<0.001
Obstructive sleep apnea syndrome	36 (3.0%)	32 (2.8%)	5 (4.0%)	0.757
Dialysis	9 (0.8%)	5 (0.4%)	2 (1.6%)	0.258
Current smoker	213 (18.0%)	174 (15.4%)	19 (15.2%)	0.217
Drug abuse	0 (0.0%)	2 (0.2%)	0 (0.0%)	0.314
Alcohol abuse	11 (0.9%)	12 (1.1%)	0 (0.0%)	0.506
Echocardiography				
Left ventricular ejection fraction, mean ± SD	59.30 ± 5.93	56.15 ± 9.37	54.67 ± 10.29	<0.001
Left atrial diameter, mean ± SD	3.85 ± 0.66	4.41 ± 0.73	4.23 ± 0.71	<0.001
Atrial fibrillation type				<0.001
Initial/new-onset	9 (0.8%)	127 (11.2%)	9 (7.3%)	
Paroxysmal	1140 (96.5%)	8 (0.7%)	64 (51.6%)	
Persistent	20 (1.7%)	614 (54.3%)	30 (24.2%)	
Permanent	11 (0.9%)	344 (30.4%)	18 (14.5%)	
Unknown	1 (0.1%)	37 (3.3%)	3 (2.4%)	
Medication at enrollment				
Antiplatelet therapy				
Aspirin	69 (5.8%)	80 (7.1%)	81 (64.8%)	<0.001
Clopidogrel	20 (1.7%)	18 (1.6%)	47 (37.6%)	<0.001
Anticoagulation therapy				
Any anticoagulation	937 (78.9%)	971 (85.8%)	108 (86.4%)	<0.001
Any anticoagulation in CHA_2DS_2-VASc ≥2 (n = 1620)	626 (87.6%)	705 (90.7%)	104 (87.4%)	0.12

(*continued*)

Table 2 (***Continued***)

Variables	Younger paroxysmal AF (N = 1190)	Persistent/permanent AF with LA enlargement (N = 1143)	Atherosclerotic comorbid AF (N = 125)	p
Other medication				
Anti-arrhythmic drug	385 (32.4%)	126 (11.1%)	14 (11.2%)	<0.001
Renin-angiotensin inhibitor	383 (32.3%)	403 (35.6%)	73 (58.4%)	<0.001
Beta-blocker	560 (47.1%)	658 (58.1%)	93 (74.4%)	<0.001
Calcium channel blocker	484 (40.8%)	426 (37.6%)	60 (48.0%)	0.044
Digoxin	43 (3.6%)	110 (9.7%)	4 (3.2%)	<0.001
Diuretics	136 (11.5%)	328 (28.9%)	46 (36.8%)	<0.001
Statin	267 (22.5%)	222 (19.6%)	89 (71.2%)	<0.001
Treatment				
Rhythm control	808 (68.3%)	472 (41.7%)	38 (30.4%)	<0.001
Prior catheter ablation	104 (8.8%)	52 (4.6%)	4 (3.2%)	<0.001
Prior surgical maze	3 (0.3%)	4 (0.4%)	0 (0.0%)	0.747
Prior atrioventricular node ablation	12 (1.0%)	3 (0.3%)	1 (0.8%)	0.082
AFEQT at baseline, mean ± SD	74.93 ± 17.75	78.00 ± 16.23	74.79 ± 16.56	<0.001

Abbreviations: AF = atrial fibrillation; SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DPB = diastolic blood pressure; HR = heart rate; AFEQT = Atrial Fibrillation Effects on Quality of Life questionnaire.

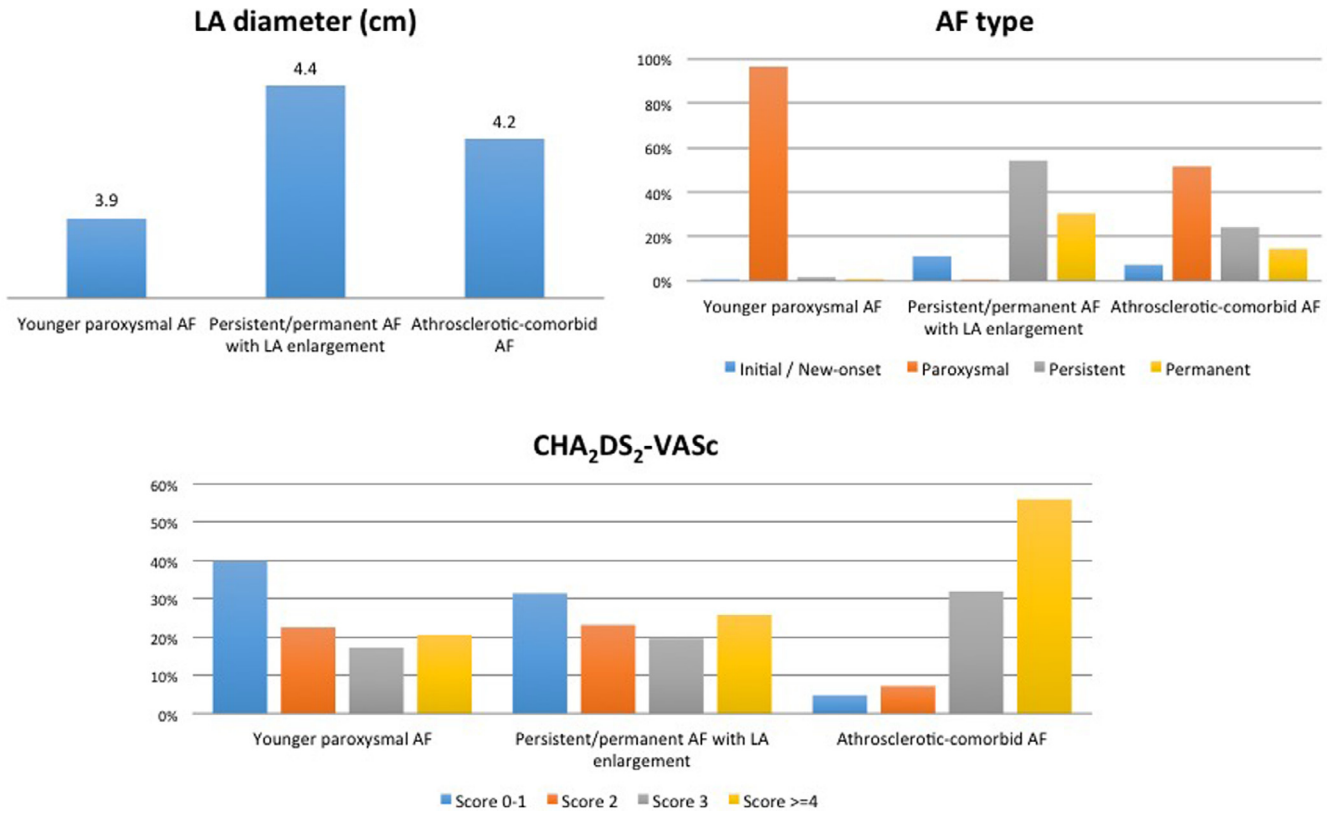

Figure 2. Relationship between the identified clusters and conventional AF classification
Abbreviation: AF=atrial fibrillation.

screen-detected AF were less likely to have symptoms and comorbidities, and more likely to have persistent/permanent AF. These features are similar to those in the persistent/permanent AF with LA enlargement cluster, suggesting that this cluster partially represents screen-detected AF. A widely prevailing health check-up system may have an impact on the formation of clusters and may have caused the difference in cluster phenotypes among countries.

Although behavioral disorders, such as alcohol abuse, drug abuse, and current smoking, and/or device implantation due to sinus node dysfunction were the main drivers to characterize clusters in the US-based study, these factors did not contribute to the differentiation of clusters in our study cohort. The precise reason is unknown, but this inconsistent discrepancy may be explained by the difference in the prevalence of these variables between datasets. In

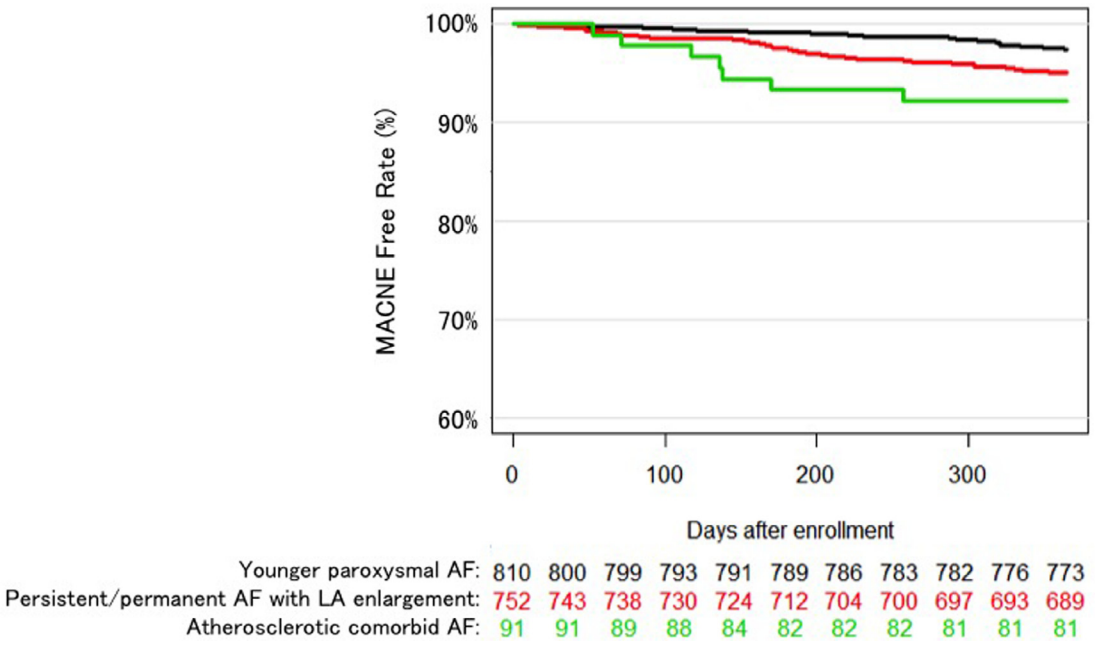

Figure 3. Kaplan-Meier curves for MACNE-free rate during the 1-year follow-up
Log-rank test shows the significant difference in MACNE among clusters (p = 0.002).
Abbreviations: MACNE= major adverse cardiovascular or neurological events; AF=atrial fibrillation.

particular, the prevalence of alcohol and drug abuse is quite lower in the Japanese cohort than in the US cohort (alcohol: 0.9% vs 3.9%; drug: 0.1% vs 1.3%), resulting in the inadequate power to characterize clusters. Similarly, the rate of device implantation is significantly lower in our dataset than in the US dataset (2.1% vs 27.6%), which is likely due to the difference in enrollment setting (outpatient only vs all-comer) and enrollment criteria (patients with a diagnosis of AF within 6 months before the initial visit for KiCS-AF vs all-comer AF patients except for AF with reversal cause and life expectancy of <6 months for ORBIT-AF), which may result in the insufficient numbers to differentiate clusters. This may indicate that clinical setting also has an important role in characterizing disease phenotypes. In addition, the difference in practice pattern between countries may also be related to the lower device implantation rate in the US. In 2009, the new pacemaker implantation rate was 61.6 per 100,000 persons in the US[13] and 23.0 per 100,000 persons in Japan,[14] which may suggest a lower threshold for implant devices in the US than in Japan.

Clinical outcomes were not significantly different among the clusters after the adjustment for CHA_2DS_2-VASc components, probably owing to the limited sample size. In addition, the greater homogeneity of our study cohort than the US-based cohort may limit the risk stratification ability. The prevalence of the key variables that significantly contributed to the cluster formation in the ORBIT-AF cohort, such as device implantation, drug abuse, and alcohol abuse, was lower in our cohort than in the ORBIT-AF cohort, which suggests the greater homogeneity of the Japanese AF patients.

There are several limitations inherent to our study and its methods. First, different clustering and linkage methods may generate different clusters. However, there is no scientific consensus on the best clustering and linkage method. Second, the ultimate number of clusters (n = 3) was at the discretion of the investigators. Incorporation of more clusters might yield different groupings; however, this may lead to the loss of power to detect differences in characteristics among clusters. Finally, with comparison between only 2 registries, it may be difficult to differentiate AF heterogeneity due to regional patient factors from that due to differences in the registries; therefore, further studies are warranted to understand AF heterogeneity.

In conclusion, 3 clinically relevant phenotypes of AF were identified through a cluster analysis of the multicenter Japanese AF registry. Conventional classifications, such as atherosclerotic risk factors and CHA_2DS_2-Vasc score, contributed to the formation of the clusters in mutually. However, in nonatherosclerotic clusters, AF type or LA size, rather than the presence or absence of behavior risk factors or sinus node dysfunction (tachy-brady syndrome), seemed to contribute to the cluster formation in the Japanese cohort, highlighting the heterogeneity among AF patients as well as regional differences between registries.

Disclosures

T Inohara: Research Grant: Boston Scientific.

JP Piccini: Research grant from Agency for Healthcare Research and Quality, ARCA biopharma, Boston Scientific, Gilead Sciences, Janssen Pharmaceuticals, Johnson & Johnson, ResMed, Spectranetics, and St Jude Medical. Consultant/Advisory Board for BMS/Pfizer, GlaxoSmithKline, Janssen Pharmaceuticals, Johnson & Johnson, Medtronic, and Spectranetics.

KW Mahaffey: Financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth- mahaffey.

K Fukuda: Research grant for Department of Cardiology, Keio University School of Medicine from Bayer Yakuhin.

S Kohsaka: Research grant for Department of Cardiology, Keio University School of Medicine from Bayer Yakuhin and Daiichi Sankyo. Advisory Board/Speaker fee from AstraZeneka, Bayer, Bristol-Myers Squibb, and Daiichi-Sankyo.

S Takatsuki: Research grant from Bayer Yakuhin and Japan Lifeline. Advisory Board/Speaker fee from Daiichi-sankyo, Bayer, Bristol-Myers Squibb, Pfizer, Behringer, Medtronic and Biotronik.

There is no other potential conflict of interests.

Acknowledgment

The authors appreciate the contributions of all the investigators and clinical coordinators involved in the KiCS-AF registry, who are listed in the Supplement.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.071.

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G. 2014 aha/acc/hrs guideline for the management of patients with atrial fibrillation: a report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2014;64:e1–76.
2. Ahmad T, Pencina MJ, Schulte PJ, O'Brien E, Whellan DJ, Pina IL, Kitzman DW, Lee KL, O'Connor CM, Felker GM. Clinical implications of chronic heart failure phenotypes defined by cluster analysis. *J Am Coll Cardiol* 2014;64:1765–1774.
3. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015;131:269–279.
4. Ahmad T, Desai N, Wilson F, Schulte P, Dunning A, Jacoby D, Allen L, Fiuzat M, Rogers J, Felker GM, O'Connor C, Patel CB. Clinical implications of cluster analysis-based classification of acute decompensated heart failure and correlation with bedside hemodynamic profiles. *PLoS One* 2016;11:e0145881.
5. Parikh KS, Rao Y, Ahmad T, Shen K, Felker GM, Rajagopal S. Novel approach to classifying patients with pulmonary arterial hypertension using cluster analysis. *Pulm Circ* 2017;7:486–493.
6. Horiuchi Y, Tanimoto S, Latif A, Urayama KY, Aoki J, Yahagi K, Okuno T, Sato Y, Tanaka T, Koseki K, Komiyama K, Nakajima H, Hara K, Tanabe K. Identifying novel phenotypes of acute heart failure using cluster analysis of clinical variables. *Int J Cardiol* 2018;262:57–63.
7. Inohara T, Shrader P, Pieper K, Blanco RG, Thomas L, Singer DE, Freeman JV, Allen LA, Fonarow GC, Gersh B, Ezekowitz MD, Kowey PR, Reiffel JA, Naccarelli GV, Chan PS, Steinberg BA, Peterson ED, Piccini JP. Association of of atrial fibrillation clinical phenotypes with treatment patterns and outcomes: a multicenter registry study. *JAMA Cardiol* 2018;3:54–63.
8. Inohara T, Kimura T, Ueda I, Ikemura N, Tanimoto K, Nishiyama N, Aizawa Y, Nishiyama T, Katsumata Y, Fukuda K, Takatsuki S, Kohsaka S. Effect of compliance to updated AHA/ACC performance and quality measures among patients with atrial fibrillation on outcome (from Japanese multicenter registry). *Am J Cardiol* 2017;120:595–600.
9. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the atrial fibrillation effect on quality-of-life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:15–25.
10. Kabacoff Robert I, 16. Cluster analysis. *R in Action: Data Analysis and Graphics with R*. Second edition. Shelter Island, NY: Manning Publications Co; 2015.
11. Inohara T, Kohsaka S, Okamura T, Watanabe M, Nakamura Y, Higashiyama A, Kadota A, Okuda N, Murakami Y, Ohkubo T, Miura K, Okayama A, Ueshima H, Group NDR. Cumulative impact of axial, structural, and repolarization ECG findings on long-term cardiovascular mortality among healthy individuals in Japan: National integrated project for prospective observation of non-communicable disease and its trends in the aged, 1980 and 1990. *Eur J Prev Cardiol* 2014;21:1501–1508.
12. Ministry of Health, Labour and Welfare. The ordinance on industrial safety and health. 2007.
13. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;60:1540–1545.
14. The Japanese Circulation Society. The Japanese Registry of All Cardiac and Vascular Disease 2011. http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2016web.pdf (Accessed on May 19, 2019).