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ORIGINAL ARTICLE
Atrial Fibrillation

Echocardiographic Structure and Function in Elderly Patients With Atrial Fibrillation in Japan
— The ANAFIE Echocardiographic Substudy —

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Background: Echocardiographic data on the cardiac structure and function in elderly patients with atrial fibrillation (AF) and heart failure (HF) are limited. This subcohort study of the ANAFIE Registry analyzed echocardiographic parameters to identify cardiac structural and functional characteristics.

Methods and Results: Of 32,726 subjects in the ANAFIE population, 1,494 (4.6%) were entered as the echocardiography subcohort. Half of the patients, including those with persistent and permanent AF, older age (≥80 years), and $CHADS_2$ score ≥2, had left atrial (LA) volume index ≥48 mL/m², indicating severe LA enlargement. LA enlargement significantly correlated with impaired LA reservoir function, regardless of age and $CHADS_2$ score. Types of AF and rhythm were strongly related to LA volume and reservoir function (P<0.0001). Moderate-to-severe mitral and tricuspid regurgitation were significantly more common, and the early diastolic mitral inflow velocity to mitral annulus velocity ratio was significantly higher among patients with than without HF history (all, P<0.0001).

Conclusions: In this subcohort, LA enlargement correlated with impaired LA reservoir function. Elderly patients with non-valvular AF and a history of HF had LA enlargement and dysfunction, increased LV mass index, low LV ejection fraction, and high heart rate.

Key Words: Atrial fibrillation; Echocardiography; Elderly; Heart failure; Left atrial function

Atrial fibrillation (AF) remains the most common arrhythmia among elderly adults. Its prevalence increases from 1% to 2% in the general population, to nearly 5% among those aged between 60 and 70 years, and to >10% among those aged ≥80 years.[1] This is of special clinical relevance in Japan, given the recent growth in the aging of the population and the increased prevalence of diseases affecting the elderly, such as AF and heart failure (HF).[2,3]

AF has been associated with the development of other cardiovascular events, including HF.[4] HF and AF are closely related pathologies. Of note, HF has been described as one of the strongest predictors of AF.[5] As with AF, the occurrence of HF also increases dramatically with advancing age, with a prevalence of >10% among individuals aged ≥70 years.[6] Among patients with AF, depending on the type of AF, the HF prevalence can range between 33% and 56%.[7] Thus, precise assessment of both systolic and dia-

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stolic function is needed to properly manage AF patients.

Echocardiography is a non-invasive, readily available, and versatile tool with a relatively low cost that allows the evaluation of cardiac structure and function of patients with AF[8] and HF.[9,10] Echocardiography provides useful and valuable information for the assessment of cardiac structure and function, risk stratification, prognosis, and follow-up of patients with AF. It is the cornerstone of management for both AF and HF[8,10] because it guides proper anticoagulation use, as well as rate and rhythm control strategies.[11] However, in AF, irregular cardiac cycle length leads to variations in left ventricular ejection fraction (LVEF) and stroke volume, particularly concerning the RR interval preceding the measurement. These factors can affect the reliability of echocardiographic parameters of patients with AF. Although the diastolic echocardiographic parameters in select AF patients have been validated, data on the validity and reproducibility of systolic indices are extremely limited.[12] This can be extrapolated to special populations that are generally excluded from clinical trials, such as elderly patients, as well as the very elderly. In fact, echocardiographic data of Japanese elderly patients with AF are scarce. Thus, the changes in echocardiographic structural and functional parameters caused by AF, and associated changes in rhythm, need to be further characterized in this population. Further, studies focusing on changes in rhythm in elderly AF patients are also scarce, especially in very elderly patients.

The prospective All Nippon AF In the Elderly (ANAFIE) Registry[13] aimed to clarify the status of anticoagulation therapy and the prognosis of patients aged ≥75 years with non-valvular AF (NVAF) in Japan.[14,15] The objective of this subanalysis of the baseline data of the ANAFIE Registry was to analyze the echocardiographic parameters of elderly patients with AF to further characterize the cardiac structural and functional changes and assess how these changes affect rhythm in these patients.

Methods

Study Design

The details of the study design have been published elsewhere.[13] Briefly, the ANAFIE Registry was a multicenter, prospective registration cohort study conducted in Japan between October 2016 and January 2020 (end of registration period: January 2018). The study was registered at UMIN Clinical Trials Registry under the identifier UMIN000024006. The ANAFIE Registry protocol was approved by The Ethics Committee of The Cardiovascular Institute, and the registry complied with the Declaration of Helsinki, local regulations, and ethical guidelines in Japan. Patients provided written informed consent for study participation. According to the observational nature of the study, patients were free to withdraw from the study at any time, and there were no study-mandated therapeutic interventions.

Patients

The main eligibility and exclusion criteria of the ANAFIE Registry have been published.[13] Enrolled patients were elderly ambulatory patients (≥75 years old) with NVAF. This subanalysis focuses on patients who consented to be involved in the echocardiographic subcohort study and underwent transthoracic echocardiography within 2 months after enrollment.

Study Measures

All echocardiographic data, including left atrial (LA) size and LV structure and function, were collected and evaluated according to the American Society of Echocardiography (ASE) guidelines.[15] Sonographers received a detailed measurement manual (based on the ASE guidelines) as well as training, after which they were able to conduct the measurements. Echocardiographic images were acquired in DICOM format. To validate the echocardiographic measurements, a central office confirmed the validity of the measured values and the images from each site, and all data were confirmed by board-certified cardiologists.

Study assessment items were as follows.[13]

(1) LV structure and function: LV end-diastolic diameter, LV end-systolic diameter, interventricular septal thickness, LV posterior wall thickness, LV end-diastolic volume, LV end-systolic volume, LVEF, LV stroke volume, LV mass (LVM) index, and LV spherical index.
(2) LA structure and function: LA enlargement and total LA emptying fraction (LAEF) calculated based on LA volume: (LA maximum volume − LA minimum volume)/LA maximum volume (i.e., LAEF = [1 − LA minimum volume]/LA maximum volume). LA conduit or passive EF: (LA maximum volume − LA pre-A volume)/LA maximum volume. LA contractile or active EF: (LA pre-A volume − LA minimum volume)/LA pre-A volume.
(3) RV structure and function: tricuspid regurgitation pressure gradient, inferior vena cava diameter, estimated right atrial pressure, tricuspid annular plane systolic excursion, tricuspid valve lateral annular velocity.
(4) Doppler method: LV inflow blood flow early diastolic wave, LV inflow blood flow atrial systolic wave, mitral annulus early diastolic velocity, mitral annulus atrial systolic velocity.
(5) Cardiac valve involvement (mitral valve, aortic valve, tricuspid valve, pulmonary valve, valve repair).

LV volume and LVEF were calculated by the biplane disk summation method. The LVM was calculated by the linear method (Cube formula) recommended by the ASE,[16] indexed to body surface area: {0.8 (1.04 ([left ventricular diastolic diameter (LVDd) + posterior wall thickness in diastole + interventricular septal thickness in diastole]^3 − [LVDd])^3) + 0.6}.

The biplane disk summation method was also used to measure LA maximum volume by using apical 4-chamber and 2-chamber views at the end-systolic frame preceding the mitral valve opening. The LA volume index (LAVi) was then indexed to the patient's body surface area. A LAVi of 34 mL/m^2 was the cutoff for enlargement or non-enlargement in this study, as per the recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography from the ASE and the European Association of Cardiovascular Imaging, with indices of 34–41, 41–48, and >48 mL/m^2 indicating mild, moderate, and severe enlargement, respectively.[17] In a similar manner, the minimum LA volume was measured at the end-diastolic frame preceding the mitral valve closure. At the onset of the electrocardiographic P-wave, we calculated the LA pre-A volume for subjects not experiencing AF at the time of echocardiography.[18]

As described in the ENGAGE TIMI-48 trial,[19] early diastolic (E) and atrial systolic (A) transmitral velocities were measured by pulsed-wave Doppler using the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflets. Peak lateral and septal mitral

Table 1. Baseline Characteristics of Patients in the Echocardiographic Subcohort and Total Cohort

	Echocardiographic subcohort	Total cohort
Patients	1,494	32,726
Age, years	80.8±4.6	81.5±4.8
75–79	696 (46.6)	13,059 (39.9)
80–84	459 (30.7)	11,103 (33.9)
85–89	274 (18.3)	6,401 (19.6)
≥90	65 (4.4)	2,163 (6.6)
Female	609 (40.8)	13,993 (42.8)
Height, cm	157.5±9.0	157.2±9.5
Weight, kg	57.8±10.7	57.8±11.2
BMI, kg/m²	23.2±3.5	23.3±3.6
SBP, mmHg	127.5±18.3	127.4±17.0
DBP, mmHg	70.3±11.7	70.6±11.6
CCr, mL/min	47.4±18.1 (n=1,231)	48.4±21.8 (n=26,498)
<15 or dialysis	29 (1.9)	428 (1.3)
≥15 to <30	172 (11.5)	3,516 (10.7)
≥30 to <50	511 (34.2)	10,886 (33.3)
≥50 to <80	481 (32.2)	10,577 (32.3)
≥80	260 (17.4)	1,122 (3.4)
Hypertension	1,086 (72.2)	24,615 (75.2)
$CHADS_2$ score	2.7±1.1	2.9±1.2
1	164 (11.0)	3,002 (9.2)
2	557 (37.3)	11,539 (35.3)
≥3	773 (51.7)	18,185 (55.6)
CHA_2DS_2-VASc score	4.3±1.4	4.5±1.4
≤3	430 (28.8)	8,500 (26.0)
4 or 5	799 (53.5)	17,279 (52.8)
≥6	265 (17.7)	6,947 (21.2)
Type of AF		
Paroxysmal	689 (46.1)	13,751 (42.0)
Persistent	244 (16.3)	5,423 (16.6)
Longstanding persistent	225 (15.1)	4,427 (13.5)
Permanent	336 (22.5)	9,125 (27.9)

Data are presented as n (%) or mean±standard deviation. AF, atrial fibrillation; BMI, body mass index; CCr, creatinine clearance; DBP, diastolic blood pressure; SBP, systolic blood pressure.

annular early diastolic (e') and atrial systolic (a') velocities were assessed using tissue Doppler imaging. Left ventricular filling pressures were estimated by E-wave divided by average e' velocities. Other assessment parameters acquired only in this subcohort were basic heart rhythm at echocardiography, heart rate, specific activity scale, New York Heart Association (NYHA) classification, B-type natriuretic peptide or N-terminal pro β-type natriuretic peptide.

Statistical Analysis

Data are presented as mean±standard deviation. Frequency tables were created for categorical variables, and summary statistics were calculated for continuous variables. For comparisons of continuous variables, a 2-sample t-test was used, and for comparisons of categorical variables, a chi-squared test was used. The Pearson product-moment correlation coefficient was used for correlation analysis. The P-trend was calculated using the Jonckheere-Terpstra test for continuous variables, the Cochran-Armitage test for 2-level categorical variables, and the Cochran-Mantel-Haenszel test correlation statistic for 3-level and higher categorical variables. No imputations were made for missing data, which were not included in the analyses. A 2-sided P value <0.05 indicated statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Tokyo, Japan).

Results

Patients' Characteristics

Of all enrolled patients (n=32,726), 1,494 with available echocardiographic data constituted this subcohort study group, and these patients were further stratified into 2 groups based on whether they had a history of HF. **Table 1** shows the baseline characteristics of patients in this subcohort, contrasted with those of the total ANAFIE Registry population. Compared with the total cohort, patients in the echocardiographic subcohort were slightly younger, had lower $CHADS_2$ and CHA_2DS_2-VASc scores, and had a higher proportion of paroxysmal AF and longstanding persistent AF.

Table 2 shows the baseline characteristics of patients according to type of AF. Younger patients (75–79 years) predominantly had paroxysmal AF and persistent AF,

Table 2. Baseline Characteristics According to Type of Atrial Fibrillation

	Paroxysmal	Persistent	Permanent	P-trend[a]
Patients	689	469	336	
Age, years				0.0001
75–79	349 (50.7)	219 (46.7)	128 (38.1)	
80–84	194 (28.2)	159 (33.9)	106 (31.5)	
85–89	120 (17.4)	73 (15.6)	81 (24.1)	
≥90	26 (3.8)	18 (3.8)	21 (6.3)	
Female	312 (45.3)	183 (39.0)	114 (33.9)	0.0003
$CHADS_2$ score				<0.0001
1	100 (14.5)	40 (8.5)	24 (7.1)	
2	286 (41.5)	163 (34.8)	108 (32.1)	
≥3	303 (44.0)	266 (56.7)	204 (60.7)	
CHA_2DS_2-VASc score				0.0017
≤3	220 (31.9)	123 (26.2)	87 (25.9)	
4 or 5	368 (53.4)	254 (54.2)	177 (52.7)	
≥6	101 (14.7)	92 (19.6)	72 (21.4)	
Comorbidities				
Heart failure[b]	159 (23.1)	180 (38.4)	150 (44.6)	<0.0001
Hypertension	494 (71.7)	338 (72.1)	254 (75.6)	0.2247
Diabetes mellitus	174 (25.3)	125 (26.7)	97 (28.9)	0.2213
Cerebrovascular disease	111 (16.1)	99 (21.1)	77 (22.9)	0.0052
Coronary artery disease	141 (20.5)	81 (17.3)	66 (19.6)	0.5658
CKD	110 (16.0)	86 (18.3)	94 (28.0)	<0.0001
Smoking, ever	223 (38.8)[c]	175 (43.3)[d]	103 (38.3)[e]	0.6897
CCr, mL/min	46.2 (35.7, 59.5)	48.4 (34.4, 59.0)	44.5 (34.5, 56.7)	0.2657
Heart rate, beats/min	65.0 (59.0, 73.0)	70.0 (61.0, 81.5)	70.0 (60.0, 80.0)	<0.0001
SBP, mmHg	128.0 (116.0, 140.0)	125.5 (112.0, 139.0)	126.0 (115.0, 137.0)	0.0344
DBP, mmHg	70.0 (62.0, 76.0)	71.0 (63.0, 79.0)	70.0 (63.0, 77.0)	0.1188

Data are presented as n (%) or median (Q1, Q3). [a]The Jonckheere-Terpstra trend test for continuous variables, the Cochran-Armitage test for 2-level categorical variables, and the Cochran-Mantel-Haenszel test correlation statistic for 3-level and higher categorical variables were used for P-trend calculations. [b]Including heart failure and left ventricular systolic dysfunction. [c]Excluded unknown (n=114). [d]Excluded unknown (n=65). [e]Excluded unknown (n=67). CCr, creatinine clearance; CKD, chronic kidney disease; DBP, diastolic blood pressure; Q quartile; SBP, systolic blood pressure.

whereas persistent AF was prominent among those aged 80–84 years (P-trend=0.0001). Permanent AF was more common among patients aged ≥85 years. A higher proportion of female patients had paroxysmal AF compared with other types of AF (P-trend=0.0003). More patients with paroxysmal AF had $CHADS_2$ score of 1 or 2, and more patients with permanent AF had a score ≥3 (P-trend <0.0001). Similarly, more patients with paroxysmal AF had CHA_2DS_2-VASc score ≤3, and more patients with permanent AF had a score ≥6 (P-trend=0.0017). Permanent AF patients presented higher proportions of HF (P-trend<0.0001), cerebrovascular disease (P-trend=0.005)], and chronic kidney disease (P-trend <0.0001) compared with patients with other AF types. Other differences were noted for heart rate (P-trend <0.0001), and systolic blood pressure (P-trend=0.03).

Table 3 shows the baseline characteristics of patients according to maximum LAVi. Overall, 51.5% of patients in the echocardiographic subcohort had a LAVi ≥48 mL/m², and 13.6% had a LAVi between 41 and <48 mL/m². Among patients with LAVi <34 and 34–<41 mL/m², more than 52% were aged between 75 and 79 years. For each age category, the number of patients with LAVi >48 mL/m² was the highest among the 4 LAVi categories. The percentages of patients with LAVi >48 mL/m² increased across AF types, with 28.2%, 35.1%, and 36.7%, in paroxysmal, permanent, and persistent AF, respectively. LAVi ≥48 mL/m² (enlarged LA) was observed in a higher proportion of patients with AF without pacemaker than for patients with sinus rhythm and AF with pacemaker and in a higher proportion of patients with $CHADS_2$ scores 2 and ≥3 than for patients with a score of 1, but the proportions were similar for patients with and without a history of HF.

Relationship Between LAVi and LAEF

There was a statistically significant (P<0.0001), negative correlation between LAVi and LAEF in the echocardiographic subcohort (r=−0.423; **Figure 1A**). The relationship between LAVi and LAEF was also compared by age range (**Figure 2A–D**). There was a moderate inverse correlation between LAVi and LAEF in all age groups, indicating that LA enlargement correlated with impaired LA reservoir function regardless of patient age. Similarly, LA enlargement correlated with impaired LA reservoir function regardless of the type of AF (**Figure 3A–C**). Compared with the persistent + longstanding persistent AF (r=−0.247) and permanent AF groups (r=−0.246), the paroxysmal AF group tended to show a correlation (r=−0.368) between LAVi and LAEF. We also analyzed the volume-function relationship in patients categorized by sinus rhythm (r=−0.299), AF without pacemaker (r=−0.112), and AF

Table 3. Baseline Characteristics According to LAVi

LAVi, max (mL/m²)	<34	34–<41	41–<48	≥48	P-trend[a]
No. of patients	261	191	176	667	
Age, years					<0.0001
75–79	145 (55.6)	100 (52.4)	90 (51.1)	279 (41.8)	
80–84	70 (26.8)	61 (31.9)	51 (29.0)	208 (31.2)	
85–89	38 (14.6)	28 (14.7)	26 (14.8)	143 (21.4)	
≥90	8 (3.1)	2 (1.0)	9 (5.1)	37 (5.5)	
Type of AF					<0.0001
Paroxysmal	203 (77.8)	119 (62.3)	92 (52.3)	188 (28.2)	
Persistent (includes longstanding)	46 (17.6)	55 (28.8)	52 (29.5)	245 (36.7)	
Permanent	12 (4.6)	17 (8.9)	32 (18.2)	234 (35.1)	
Type of rhythm[b]	n=260	n=189	n=174	n=657	<0.0001
Sinus rhythm	205 (78.8)	112 (59.3)	84 (48.3)	141 (21.5)	
AF without pacemaker	32 (12.3)	59 (31.2)	69 (39.7)	438 (66.7)	
AF with pacemaker	2 (0.8)	2 (1.0)	6 (3.4)	41 (6.1)	
$CHADS_2$ score					<0.0001
1	53 (20.3)	27 (14.1)	13 (7.4)	55 (8.2)	
2	104 (39.8)	71 (37.2)	75 (42.6)	224 (33.6)	
≥3	104 (39.8)	93 (48.7)	88 (50.0)	388 (58.2)	
History of HF					<0.0001
Present	61 (23.4)	61 (31.9)	73 (41.5)	335 (50.2)	
Absent	200 (76.6)	130 (68.1)	103 (58.5)	332 (49.8)	

Data are shown as n (%). [a]Cochran-Armitage test for 2-level categorical variables, and the Cochran-Mantel-Haenszel test correlation statistic for 3-level and higher categorical variables were used for P-trend calculations. [b]At the time of the echocardiographic recording. AF, atrial fibrillation; HF, heart failure; LAVi, left auricular volume index.

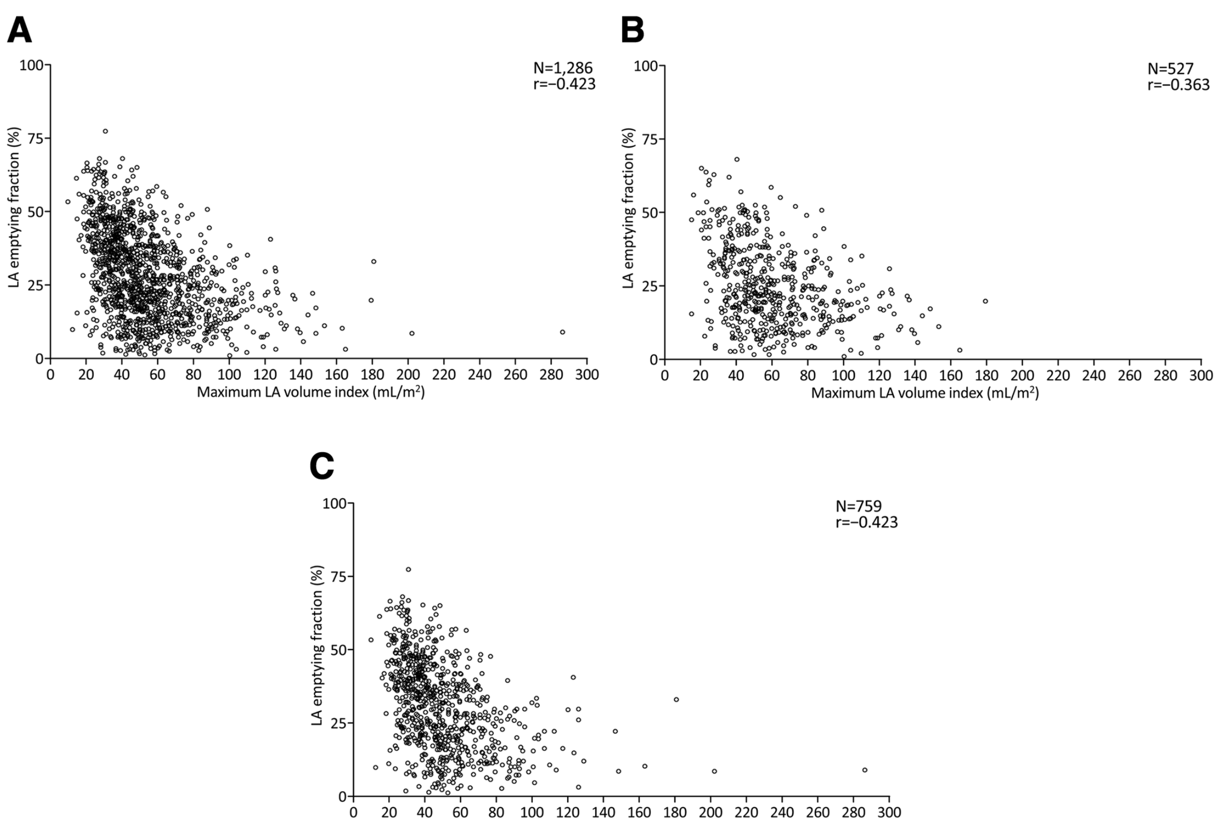

Figure 1. Relationship between LA emptying fraction and LA volume index (**A**) in the total subcohort; by presence (**B**) and absence (**C**) of heart failure. LA, left atrial.

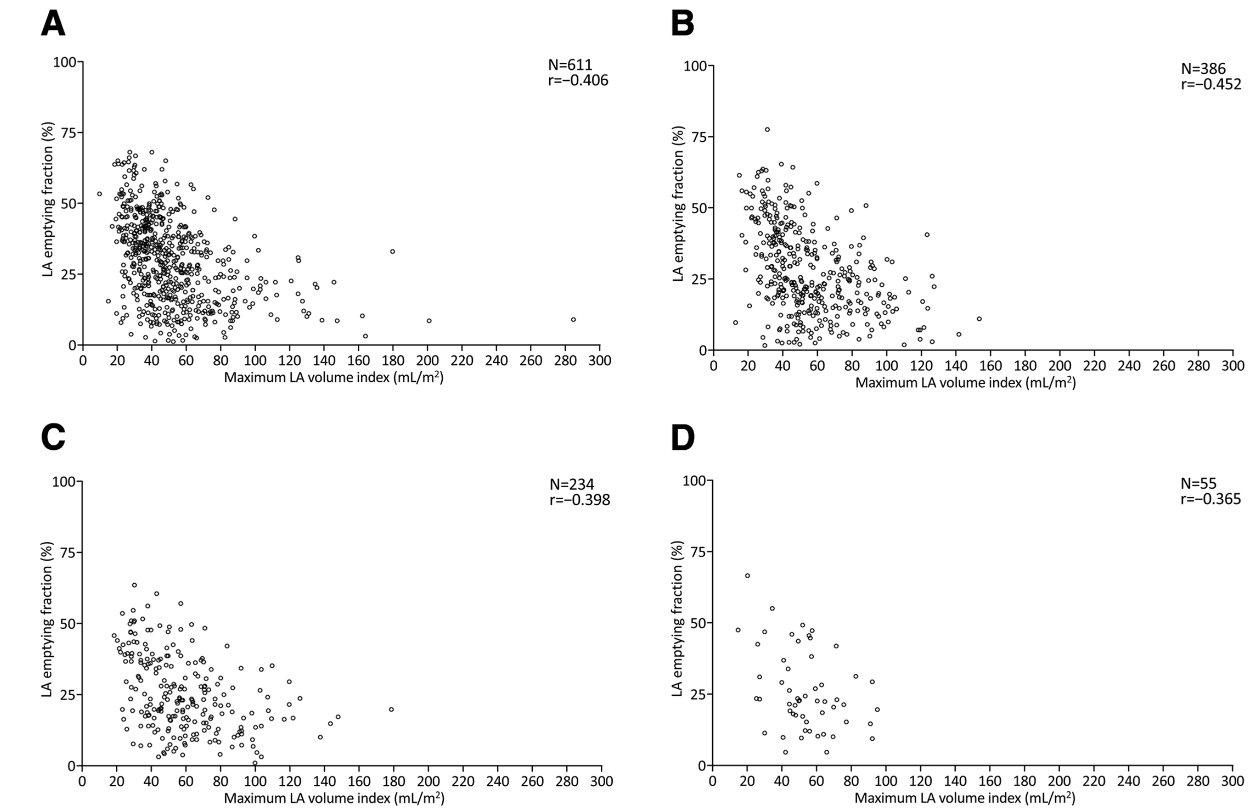

Figure 2. Relationship between LA emptying fraction and LA volume index in patients with NVAF by age: (**A**) 75–79 years, (**B**) 80–84 years, (**C**) 85–89 years and (**D**) ≥90 years. LA, left atrial; NVAF, non-valvular atrial fibrillation.

with pacemaker (r=−0.022) (**Figure 4A**–**C**). It was not possible to compare differences among all 3 groups (sinus rhythm vs. AF without pacemaker vs. AF with pacemaker), but there was a significant difference (P<0.0001) between patients with AF without pacemaker and those with AF plus pacemaker. Similar analyses of the volume-function relationship were conducted by $CHADS_2$ score of 1 (r=−0.491), 2 (r=−0.419), and ≥3 (r=−0.392) (**Figure 5A**–**C**).

History of HF

In this subcohort, 611 (40.9%) patients had a history of HF. A total of 181 (29.6%) patients were classified as NYHA functional class I, 227 (37.2%) as class II, 53 (8.7%) as class III, and 2 (0.3%) as class IV. Patients had a metabolic equivalent of 4.7±1.8, and a mean duration of illness of 5.5±5.1 years. In total, 11.1% (n=68) had unknown history of hospitalization, 39.0% (n=238) had no history and 49.9% (n=305) had a history of hospitalization.

The echocardiographic characteristics of the LV according to the presence or absence of a history of HF, age, and $CHADS_2$ score are shown in **Supplementary Table 1**. When the echocardiographic characteristics of the LV were compared by history of HF, there were significant differences in all parameters except for LV length. Left ventricular end-diastolic and -systolic volume indices were significantly higher in the HF history group compared with the group without HF history. The LVEF (Teichholz formula) was 59.7±12.3% and 65.1±8.8% in the groups with HF history and without HF history, respectively (P<0.0001). LVEF results by group using the method of disks were similar. Patients with a history of HF had a greater mean LVM than those without a history of HF. Significantly more patients without HF history (50.1%) had sinus rhythm compared with those with a history of HF (28.0%; P<0.0001). In this subcohort, 4.0% of patients with AF had a pacemaker and 46.9% had no pacemaker. By type of rhythm, significantly more patients with history of HF (57.1%) did not have a pacemaker compared with those with a history of HF (39.8%). The mean and median values of the echocardiographic characteristics of the LV were similar across all age categories and $CHADS_2$ scores.

Echocardiographic characteristics of the LA by history of HF, age, and $CHADS_2$ score are summarized in **Supplementary Table 2**. The overall mean maximum LA volume index was 54.2±25.8 mL/m². Among patients with a history of HF, the mean maximum LA volume index was significantly increased compared with that of patients without a history of HF (P<0.0001). Patients with a history of HF also had a significantly higher minimum LA volume compared with those without a history of HF (73.3 mL vs. 58.1 mL; P<0.0001). The total LAEF for the subcohort was decreased to 28.2±15.0%. For those with and without HF history, the total LAEF was significantly different (P<0.0001). The mean and median values of the echocardiographic characteristics of the LA were also similar across all age categories and $CHADS_2$ scores.

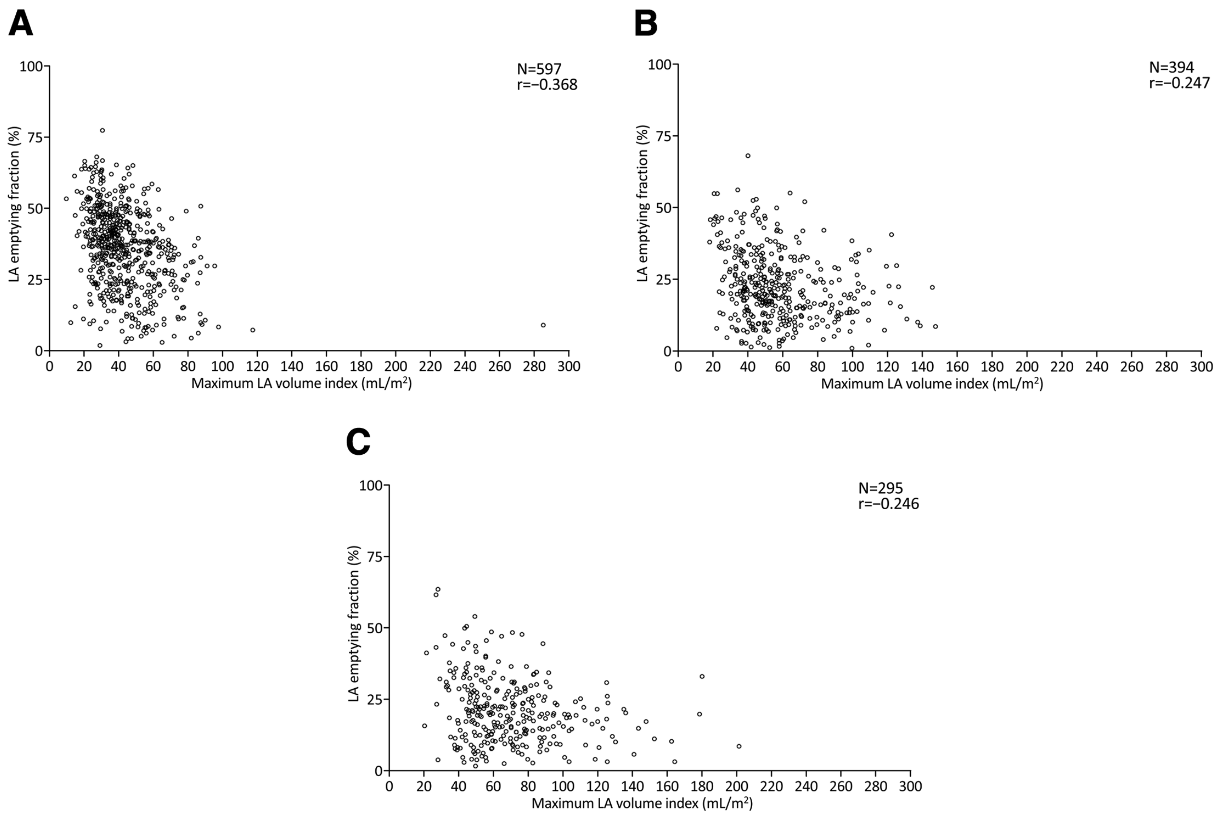

Figure 3. Relationship between LA emptying fraction and LA volume index by type of AF: (**A**) paroxysmal, (**B**) persistent + longstanding persistent, and (**C**) permanent. AF, atrial fibrillation; LA, left atrial.

Regarding the echocardiographic characteristics of the right ventricle (RV) in patients with vs. without a history of HF, the tricuspid regurgitation peak gradient (29.1±10.9 vs. 25.2±7.7 mmHg), inferior vena cava diameter (1.6±0.7 vs. 1.5±0.5 cm), and estimated pulmonary artery pressure (34.0±12.5 vs. 29.2±8.5 mmHg) were significantly greater (all, P<0.0001) among patients with a history of HF. Conversely, tricuspid annular plane systolic excursion (1.8±0.5 vs. 2.0±0.5 cm), and tissue Doppler-derived tricuspid lateral annular systolic velocity (10.5±3.0 vs. 11.3±3.2 cm/s) were significantly lower (each, P<0.0001) among patients with a history of HF vs. those without a history of HF.

In the entire subcohort, moderate-to-severe mitral regurgitation was observed in 13.6% (203/1,494) of patients, and 22.6% (337/1,494) had moderate-to-severe tricuspid regurgitation. Among patients with HF history, significantly greater percentages of patients had moderate-to-severe mitral regurgitation (20.5% [125/611]; P<0.0001) and moderate-to-severe tricuspid regurgitation (30.8% [188/611]; P<0.0001), compared with patients without HF history (mitral regurgitation: 8.8% [78/883] and tricuspid regurgitation: 16.9% [149/883]).

Significant differences were observed in some of the evaluated Doppler echocardiographic parameters between patients with and without a history of HF (**Supplementary Table 3**). Early mitral inflow velocity (E) and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') were significantly greater in patients with a history of HF compared with patients without a history of HF (P<0.0001 for all variables). The relationship between LAVi and LAEF compared among patients with a history of HF and without HF is shown in **Figure 1B**,**C**, respectively). A significant inverse relationship was observed between LAVi and LAEF by the presence of HF (r=−0.363), or absence of HF (r=−0.423), as with other parameters studied. Of note, the mean and median values of the Doppler echocardiographic parameters were largely similar across all age categories and $CHADS_2$ scores.

Discussion

In this subcohort study of the ANAFIE Registry, we analyzed echocardiographic parameters to further characterize cardiac structural and functional changes among elderly patients with NVAF with and without a history of HF. In general, the baseline clinical characteristics of the patients in the echocardiographic subcohort were similar to those of the total cohort of patients from ANAFIE. However, we noted slight differences in age, $CHADS_2$ and CHA_2DS_2-VASc scores, and the proportions of paroxysmal AF and longstanding persistent AF. By type of AF, patients with paroxysmal AF tended to be younger (<80 years of age) and have lower risk scores (scores of 1 to 2), whereas patients with permanent AF tended to be older (≥85 years old) and were at higher risk (score ≥3 or ≥6).

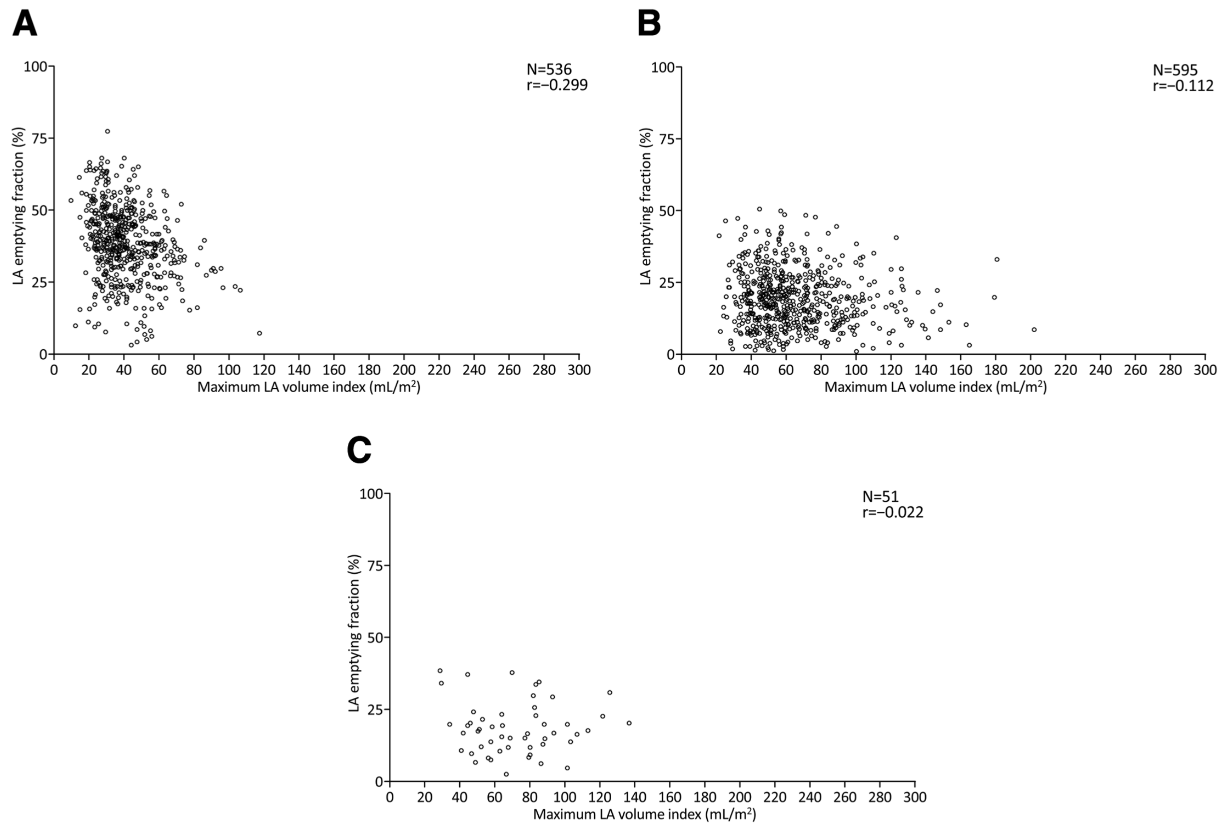

Figure 4. Relationship between LA emptying fraction and LA volume index by rhythm: (**A**) sinus rhythm, (**B**) AF without pacemaker, and (**C**) AF with pacemaker. AF, atrial fibrillation; LA, left atrial.

The main findings of this subcohort study pertained to LA size and reservoir function. Slightly over half of the patients in the subcohort had a LAVi ≥48 mL/m², indicating an enlarged LA. Greater proportions of patients with persistent and permanent AF, older age, $CHADS_2$ score ≥2, and AF (rather than sinus rhythm) had a LAVi ≥48 mL/m². We also identified a strong and significant inverse correlation between LAVi and LAEF for the total subcohort, as well as by age, paroxysmal AF, $CHADS_2$ scores, and history of HF. Of the correlations analyzed, LA enlargement correlated with impaired LA reservoir function regardless of age and $CHADS_2$ score, but there tended to be a correlation between volume and function (LAVi and LAEF) among patients with paroxysmal AF and patients categorized by rhythm (i.e., sinus rhythm, and AF with and without pacemaker).

Other relevant findings pertained to comparisons of structural and functional characteristics of NVAF patients with a history of HF vs. no history of HF. Patients with a history of HF had a lower LVEF (Teichholz formula and method of disks) compared with patients without HF (59.7% and 57.3% vs. 65.1 and 63.1, respectively). Patients with HF history also had a lower rate of sinus rhythm and a higher rate of AF compared with patients without HF history. It has been reported that both minimum and maximum LA volumes are predictive of the development of first AF or flutter in older patients without valvular heart disease or a history of atrial arrhythmia.[20] In the present study, both the minimum and maximum LA volumes were significantly higher among patients with a history of HF vs. those without (P<0.0001 for both). The prevalence of mitral regurgitation and tricuspid regurgitation was higher among patients with HF history compared with patients without HF history. The E/e' ratio in patients with a history of HF was >13 and was significantly higher than in those without a history of HF (13.2±5.9 vs. 11.5±4.9; P<0.0001). Elderly patients with HF and NVAF showed LA enlargement and dysfunction and had a significantly larger LVM compared with those without a history of HF. The increased LVM with elevated LV filling pressures (as suggested by the high E/e' ratio) is consistent with the volume overload present in HF.

The ENGAGE AF-TIMI 48 study found that most patients (55%) with AF had an enlarged LA and decreased LAEF.[17] Similarly, most patients with AF in this ANAFIE Registry subcohort presented with LA enlargement, and those with NVAF and history of HF had lower LAEF. There was an inverse relationship between LAEF and LA size in AF groups both with and without HF, and this finding was also similar to that reported in the ENGAGE AF-TIMI 48 study.[19] In contrast with the ENGAGE AF-TIMI 48 data,[19] the proportion of patients with moderate or severe mitral regurgitation was slightly higher in this subcohort (ENGAGE AF-TIMI 48, 10.8% vs. ANAFIE, 13.6%). We compared the echocardiographic features of the LV by rhythm. As in ENGAGE AF-TIMI 48, most

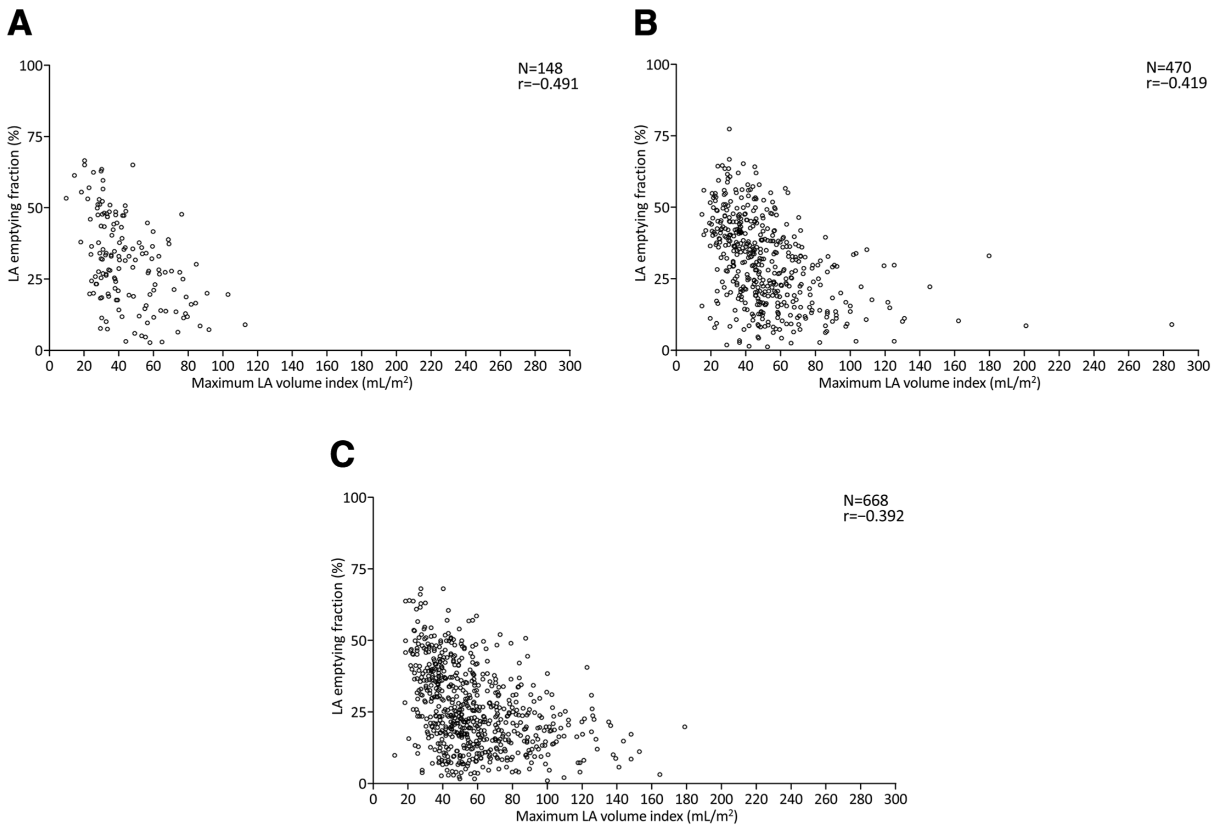

Figure 5. Relationship between LA emptying fraction and LA volume index by CHADS2 score: (**A**) 1, (**B**) 2, and (**C**) ≥3. LA, left atrial.

patients with AF had an enlarged LA, even those with sinus rhythm, but the proportion of patients with LA enlargement was even greater among patients with AF but no pacemaker. Further, significantly greater proportions of patients with a history of HF (57.1%) did not have a pacemaker compared with those with a history of HF (39.8%). Although the presence or absence of HF correlated with LA reservoir function,[21] some studies have reported that maintenance of sinus rhythm might have a greater effect on the suppression of LA enlargement and the maintenance of LA reservoir function.[22–25]

This study targeted elderly NVAF patients, and in this population it is expected that LA reservoir function will be enhanced to compensate for the physiological impairment of LV relaxation due to aging. Of note, in our sample there were many cases of low emptying fraction despite the small size of the LA. Low emptying fraction, with small LAVi, decreased LAEF, and decreased diastolic function, is considered an important indicator of AF progression. A recent study on the effects of LA size and total atrial emptying fraction in AF progression (i.e., persistent AF and low-voltage areas) showed that age and total LAEF were significantly associated with AF progression.[26] Thus, it is possible that the low emptying fraction (despite the small LAVi) is a sign of AF progression in these patients.

An E/e' ratio >13 is a strong predictor of death, and increased LVM was associated with all-cause death in the ENGAGE AF-TIMI 48 echocardiographic substudy.[18] Of note, NVAF patients with a history of HF in the present subcohort also had an E/e' ratio >13 and a significantly larger LVM compared with those without a history of HF.

Recent echocardiographic studies in patients with HF and AF showed that changes in the functional echocardiographic measures of LA and LV were associated with prognosis, clinical risk scores, incident AF and CVD, recurrent AF, or stroke.[27–30] Along the lines of previous studies, the present findings suggest that it is necessary to carefully assess not only LA size but LA reservoir function when evaluating patients with AF. Although LA size and LA reservoir function are similar and may yield similar information, evaluating LA reservoir function may be helpful not only for assessing the risk of death and other complications, such as stroke, but also for the management of AF. With an increasing atrial size, stretching causes the muscles to degenerate and lose contractile force, and the indicators related to atrial function are affected. However, it is not easy to estimate exactly when these events take place. They do not occur in isolation and changes in the LAVi will also be affected by LV diastolic function. In our sample of patients, LV function was maintained, and thus the effect of atrial size was considered negligible. However, LA reservoir function is important because it may reveal alterations in the LA prior to structural changes, such as changes in the LAVi. Thus, we consider that both anatomical and functional LA changes in AF can contribute to further understanding of the mechanisms underlying this disease and prediction of its outcomes. Furthermore, the present findings also highlight the importance of evaluating and reporting LV size and LV filling pressures among patients with AF.

Study Limitations

This echocardiographic subcohort study of the ANAFIE Registry has several potential limitations that should be acknowledged. First, it was based on baseline characteristics and did not account for clinical outcome data of stroke or systemic thromboembolism. However, we plan to evaluate the association of these parameters and outcomes in upcoming research. Second, the total ANAFIE Registry cohort was not included in this subcohort study. However, we consider that the data of this subcohort are representative of the total cohort because both groups of patients had similar characteristics. Third, it is difficult to evaluate the exact onset of AF; thus, we referred to the mean disease duration for our analyses. However, it was stipulated in the protocol of this study that a typical measurement of 1 heartbeat was sufficient, and image data were collected for 5 s and validated against values measured by random sampling. When performing echocardiography during AF, the type of measurement used is particularly important because the RR interval is irregular. Additionally, in patients with paroxysmal AF, this rhythm can affect generalization; thus, whether the results of this analysis are representative of the clinical situation of all patients in this age group warrants further investigation. Finally, as there was no central inspection agency, there were variations among the facilities. As a countermeasure, participating centers agreed to support standardization of echocardiographic measurements. Echocardiography examination items were based on the guidelines of the ASE[31] and those of the Clinical Application of Echocardiography (JCS 2010).

Conclusions

Elderly patients with NVAF from the ANAFIE Registry showed LA enlargement and LA dysfunction with increased LVM and higher filling pressures. Patients with a history of HF had a lower rate of sinus rhythm and a higher rate of AF compared with patients without HF history. It is necessary to carefully assess not only LA size but also LA reservoir function, as well as LV size and LV filling pressures, when evaluating patients with AF.

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IRB Information

Ethical approval was obtained from all relevant institutional review boards, and all patients provided written informed consent and were free to withdraw from the registry at any time. The name of the principal ethics committee was The Ethics Committees of The Cardiovascular Institute (Tokyo, Japan) and the approval number was 299.

Author Contributions

H.I., T. Yamashita, M.A., H.A., T.I., Y.K., K.O., W.S., K.T., A.H., M.Y., T. Yamaguchi, and H.T. designed and conducted the study; K.H., H.K., G.K., and H.T. interpreted the data analysis; S.T. carried out statistical analyses; K.H., H.K., G.K., T.K., J.K., A.T., and H.T. wrote and reviewed the manuscript; all authors revised and commented on the manuscript, and approved the final version.

Data Availability

1. Will the individual deidentified participant data (including data dictionaries) be shared?
   → Yes
2. What data in particular will be shared?
   → Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).
3. Will any additional, related documents be available? If so, what is it? (e.g., study protocol, statistical analysis plan, etc.)
   → Study Protocol
4. When will the data become available and for how long?
   → Ending 36 months following article publication.
5. By what access criteria will the data be shared (including with whom)?

→ Researchers who provide a methodologically sound proposal. But the proposal may be reviewed by a committee led by Daiichi-Sankyo.

6. For what types of analyses, and by what mechanism will the data be available?

→ Any purpose, Proposals should be directed to yamt-tky@cvi.or.jp

To gain access, data requestors will need to sign a data access agreement.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-21-0180