Usefulness of Left Atrial Volume as an Independent Predictor of Development of Heart Failure in Patients With Atrial Fibrillation

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Left atrial (LA) volume is known as a robust predictor of heart failure (HF) development in patients with sinus rhythm. However, among patients with atrial fibrillation (AF), the utility of LA volume for prediction of HF development has not been determined. The objective of this study was to investigate the utility of LA volume for prediction of HF development in patients with AF. Among adult patients who were referred for transthoracic echocardiography, those with AF at the baseline echocardiography were included and prospectively followed up to new-onset HF events. Patients who had significant valvular heart disease, congenital heart disease, or reduced left ventricular (LV) ejection fraction were excluded. Cox-proportional hazards models were used to assess the risk of HF development. Of a total of 562 patients, 422 (mean age 69.6 ± 9.7 years, 66.1% men) met study criteria, and 52 (12.3%) developed HF during a mean follow-up of 55 ± 43 months. Patients with HF events had larger indexed LA volume, compared with those without HF events (69 ± 46 vs 50 ± 23 ml/m^2, p <0.0001). In a multivariable analysis adjusted for other co-morbidities, LA volume was a significant predictor for HF development [per 10 ml/m^2; hazard ratio (HR) 1.14, 95% confidence interval (CI) 1.06 to 1.22, p <0.001], independently of age (per 10 years; HR 1.71, 95% CI 1.16 to 2.52, p <0.01), LV ejection fraction (per 10%; HR 0.67, 95% CI 0.52 to 0.86, p <0.01), and indexed LV mass (per 10 g/m^2; HR 1.13, 95% CI 1.03 to 1.24, p <0.05). Also, LA volume had an incremental effect for prediction of HF development to these conventional risk factors (p <0.0001). In conclusion, LA volume provides prognostic information for the prediction of future HF events in patients with AF. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:1430−1435)**

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and is associated with serious clinical consequences such as stroke, heart failure (HF), and increased mortality.[1−5] Recently, risk stratification and prevention of stroke in AF patients has been established along with therapeutic advances.[2,6,7] However, the incidence and mortality risk of HF after diagnosis of AF has not been reduced.[2,4] Therefore, prediction of HF development in patients with AF is important for risk stratification in clinical practice. In patients with sinus rhythm, left atrial (LA) volume is known to as a powerful predictor of future HF development.[1,8,9] In contrast, among patients with AF, the utility of LA volume for prediction of consequent HF development remains less clear. The objectives of our present study were to determine whether LA volume independently predicts future HF events in patients with AF, and whether it is incremental to conventional risk factors for identifying patients at increased risk of future HF events.

Methods

Among adult patients referred for transthoracic echocardiography from July 2007 to December 2008, who had AF were considered for inclusion in this study. Patients with a history of significant valvular heart disease, congenital heart disease, pacemaker/implantable cardioverter defibrillator implantation, pericardial disease, previous cardiac surgery, or reduced LV systolic function (i.e., LV ejection fraction <40%) were excluded. Significant valvular heart disease was defined as ≥ moderate aortic or mitral valve stenosis or regurgitation at the baseline echocardiographic examination. Of a total of 562 patients, 136 were excluded according to the exclusion criteria. We also excluded 4 patients who did not have optimal views for LA volume measurement, and thus study patients consisted of the remaining 422 patients. AF was defined as the electrocardiographically confirmed irregular rhythm with disorganized atrial activity and without discrete P-wave lasts at least 30 seconds. All study patients were followed forward up to the date of the occurrence of new HF events, death, or the last clinical visit until July 2017.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori

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approval by the Institutional Review Board of Kansai Medical University, Osaka, Japan, and informed consent was obtained from all patients.

Clinical data including age, gender, height, weight, heart rate, brachial blood pressure, history of co-morbidities, and medication use were recorded at the time of baseline echocardiography.

We defined the outcome of interest as new-onset of HF evens. HF was ascertained based on the Framingham criteria,[10] which requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Type of AF was classified as paroxysmal when there were recognizable intervening episode of sinus rhythm, and as persistent AF when there were no episode of sinus rhythm. Systemic hypertension was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg on ≥2 occasions that was not associated with acute illness or injury, or the use of antihypertensive therapy. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl, a random glucose level ≥200 mg/dl, or the use of insulin or medication for diabetes. Dyslipidemia defined as fasting low-density lipoprotein cholesterol level ≥140 mg/dl, fasting high-density lipoprotein cholesterol level <40 mg/dl, or fasting triglyceride level ≥150 mg/dl on ≥2 occasions, or the use of antidyslipidemic drugs. HF and myocardial infarction were defined according to the Framingham criteria.[10] Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2 on ≥2 occasions.

All transthoracic echocardiography was performed with patients in the left lateral decubitus position according to the recommendation of the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[11] and interpreted by 1 echocardiologist who was masked from clinical data. LV dimensions, LV wall thickness and LA dimension were obtained from 2-dimensional echocardiography in parasternal long-axis view. LV ejection fraction was calculated using quantitative 2-dimensional biplane modified Simpson's method. LV mass was calculated with validated formula[12] and was indexed to body surface area. LA volume was calculated using the biplane area-length formula: LA volume = $(8/3\pi \times$ 4-chamber area × 2-chamber area)/length[11] in end-systole and was indexed to body surface area. Pulse-wave Doppler examination was performed to obtain peak mitral inflow velocity at early diastole (*E*) and *E* deceleration time in apical long-axis view. Tissue Doppler echocardiography was performed with the sample volume positioned at the septal mitral annulus to obtain peak early diastolic myocardial tissue velocities (*E'*), and the *E/E'* ratio was calculated.

Baseline characteristics were summarized in terms of means and standard deviations for continuous variables, or frequency numbers and percentage for categorical variables. Differences between the 2 groups were estimated with 2-sample *t* tests for continuous variables or chi-square analyses for categorical variables. Cox proportional hazards models were used to adjust for the effect of differences in baseline characteristics or pertinent covariates on outcomes. We estimated univariable models as well as multivariable models, and hazard ratios (HRs) and their relative 95% confidence intervals (CIs) were derived. Covariates selected for multivariable models were based on significant variables at the univariable analyses, and entered models in a stepwise manner. The Kaplan-Meier method tested for differences in the HF event-free rate in 3 groups based on the indexed LA volume category (indexed LA volume ≤40 ml/m^2, 40 to 60 ml/m^2, >60 ml/m^2) by the log-rank test, and cumulative event-free survival curves depicted graphically. To evaluate the incremental prognostic value of LA volume, the global log-likelihood ratio chi-square statistics for models were determined by Cox proportional hazards regression using (1) age, LV ejection fraction, and indexed LV mass; and (2) a combination of age, LV ejection fraction, indexed LV mass, and indexed LA volume. All statistical analyses were performed using the IBM SPSS Statistics software version 24.0 (SPSS Inc., IBM, Somers, New York). All tests of significance were 2-tailed, and p value <0.05 was considered statistically significant.

Results

Of a total of 422 patients (mean age 69.6 ± 9.7 years, 66.1% men), 52 (12.3%) developed at least 1 new HF event during a mean follow-up of 55 ± 43 months. Baseline characteristics of all study patients, as well as stratified by HF event status are summarized in Table 1. In echocardiographic variables, patients who had new HF events were more likely to have larger LV end-systolic dimension, lower LV ejection fraction, higher LV end-diastolic septal and posterior wall thickness, higher indexed LV mass, and larger indexed LA volume. Patients who had new HF events were more likely to be prescribed with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or diuretics at the baseline echocardiography.

Age- and gender-adjusted univariable analyses and covariate-adjusted multivariable analyses for prediction of HF development were shown in Table 2. In age- and gender-adjusted univariable analysis, advancing age, history of HF, larger LV end-systolic dimension, lower LV ejection fraction, higher septal and posterior wall thickness, higher indexed LV mass, and larger LA volume, and larger indexed LA volume were significantly associated with new HF events. Type of AF (i.e., paroxysmal or persistent) was not significantly associated with HF development. In a multivariable model adjusted for co-morbidities and echocardiographic variables, advancing age (per 10 years; HR 1.71, 95% CI 1.16 to 2.52, p <0.01), lower LV ejection fraction (per 10%; HR 0.67, 95% CI 0.52 to 0.86, p <0.01), higher indexed LV mass (per 10 g/m^2; HR 1.13, 95% CI 1.03 to 1.24, p <0.05), and larger indexed LA volume (per 10 ml/m^2; HR 1.14, 95% CI 1.06 to 1.22, p <0.001) were significant independent predictors of new HF events. History of HF was not statistically significant after adjusting for clinical and echocardiographic variables.

The Kaplan-Meier estimated cumulative HF event-free survival stratified by indexed LA volume category (indexed LA volume ≤40 ml/m^2, 40 to 60 ml/m^2, >60 ml/m^2) were shown in Figure 1. There were stepwise increases in risk of new HF events with each increment of indexed LA volume category (Log-rank p <0.01). Estimated 5-year and 8-year HF event-free survival rate of each group (indexed LA volume <40 ml/m^2, 40 to 60 ml/m^2, >60 ml/m^2) was 95%, 89%, 86%, and 87%, 80%, 67%, respectively.

Table 1
Baseline characteristics of study patient stratified by HF event status

Variables	Overall (n = 422)	Heart failure event	
		No (n = 370)	Yes (n = 52)
Clinical			
Age (years)	69.6 ± 9.7	69.2 ± 9.9	72.0 ± 8.3
Men	279 (66.1%)	246 (66.5%)	33 (63.5%)
Body surface area (m^2)	1.61 ± 0.19	1.61 ± 0.19	1.59 ± 0.17
Body mass index (kg/m^2)	23.2 ± 3.5	23.2 ± 3.6	23.4 ± 3.4
Heart rate (beats/min)	77 ± 15	77 ± 15	79 ± 16
Systolic blood pressure (mm Hg)	124 ± 17	124 ± 17	121 ± 15
Diastolic blood pressure (mm Hg)	74 ± 12	74 ± 12	71 ± 9
Persistent atrial fibrillation	248 (58.8%)	214 (57.8%)	34 (65.4%)
Hypertension	261 (61.8%)	229 (61.9%)	32 (61.5%)
Diabetes mellitus	99 (23.5%)	85 (23.0%)	14 (26.9%)
Dyslipidemia	138 (33.3%)	118 (32.4%)	20 (39.2%)
Prior history of myocardial infarction	24 (5.7%)	20 (5.4%)	4 (7.7%)
Prior history of HF	38 (9.0%)	29 (7.8%)	9 (17.3%)
Chronic kidney disease	172 (40.8%)	143 (38.6%)	29 (55.8%)
Echocardiographic			
LV end-diastolic dimension (mm)	48.5 ± 5.6	48.4 ± 5.6	49.3 ± 5.5
LV end-systolic dimension (mm)	29.8 ± 5.7	29.5 ± 5.6	31.4 ± 6.1*
LV ejection fraction (%)	66.7 ± 9.7	67.1 ± 9.4	63.3 ± 11.1*
LV end-diastolic septal wall thickness (mm)	9.3 ± 1.7	9.2 ± 1.6	10.0 ± 2.0*
LV end-diastolic posterior wall thickness (mm)	9.1 ± 1.4	9.0 ± 1.4	9.6 ± 1.3*
Indexed LV mass (g/m^2)	88.7 ± 25.5	87.1 ± 23.9	100.3 ± 33.0*
LA dimension (mm)	45.5 ± 8.6	45.3 ± 8.5	47.4 ± 9.2
LA volume (mL)	83.5 ± 43.3	79.9 ± 36.8	108.9 ± 70.5*
Indexed LA volume (ml/m^2)	52.3 ± 27.4	49.9 ± 22.7	69.0 ± 46.2*
Mitral inflow Doppler induces			
E (cm/s)	84.7 ± 24.4	84.9 ± 23.9	83.3 ± 28.5
E deceleration time (ms)	194 ± 73	194 ± 73	193 ± 72
Tissue Doppler imaging			
E'	7.8 ± 3.3	7.9 ± 3.4	6.9 ± 2.2
E/E'	11.6 ± 4.4	11.6 ± 4.6	12.3 ± 3.3
Medication			
ACE-I or ARBs	176 (41.7%)	142 (38.4%)	34 (65.4%)*
Beta-adrenergic antagonists	137 (32.5%)	117 (31.6%)	20 (38.5%)
Diuretics	115 (27.3%)	92 (24.9%)	23 (44.2%)*
Calcium channel blockers	186 (44.1%)	160 (43.2%)	26 (50.0%)
Antihyperlipidemic agents	91 (21.6%)	79 (21.4%)	12 (23.1%)
Anticoagulants	201 (47.6%)	170 (45.9%)	31 (59.6%)
Antiplatelets	167 (39.6%)	146 (39.5%)	21 (39.6%)
Digitalis	115 (27.3%)	97 (26.2%)	18 (34.6%)

Values are given as mean ± SD or number (%).
Differences were evaluated with chi-square analyses (categorical variables) and 2-sample *t* tests (continuous variables).
ACE-I = angiotensin-converting enzyme-inhibitors, ARBs = angiotensin receptor blockers, HF = heart failure, LA = left atrial, LV = left ventricular.
* $p < 0.05$ versus patients with no HF events.

The global log likelihood ratio chi-square statistics for the models containing (1) age, LV ejection fraction, and indexed LV mass; and (2) age, LV ejection fraction, indexed LV mass, and indexed LA volume were shown in Figure 2. The predictive power of the models showed that indexed LA volume had an incremental effect for prediction of HF development to age, LV ejection fraction, and indexed LV mass ($p < 0.0001$).

Discussion

In this prospective AF cohort study, we investigated the clinical utility of LA volume for prediction of HF development. Our study showed that indexed LA volume was a strong predictor of HF development, independently of and incremental to age, LV ejection fraction, and indexed LV mass, which are conventional risk factors. Further, there were stepwise increases in risk of HF development with an increment of indexed LA volume category.

AF is the most common sustained arrhythmia in clinical practice and is associated with serious clinical consequences such as stroke, HF, and increased mortality.[1–5] The 5-year cumulative incidence of HF after the first diagnosis of AF is reported around 20%, which is higher than that of stroke, and the mortality risk was 3.4-fold higher after HF compared with no evidence of HF.[4,13] In recent years, risk stratification and prevention of stroke in AF patients has been established along with therapeutic advances as well as

Table 2
Univariable and multivariable models for prediction of HF events

Variables	HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Clinical				
Age (per 10 years)	1.70 (1.19, 2.43)	<0.01	1.71 (1.16, 2.52)	<0.01
Men	0.99 (0.56, 1.75)	0.98		
Body surface area (per 0.1 m^2)	0.98 (0.81, 1.20)	0.86		
Body mass index (kg/m^2)	1.02 (0.94, 1.11)	0.61		
Heart rate (per 10 beats/min)	1.12 (0.93, 1.35)	0.22		
Systolic blood pressure (per 10 mm Hg)	0.91 (0.75, 1.09)	0.28		
Diastolic blood pressure (per 10 mm Hg)	0.86 (0.66, 1.11)	0.24		
Persistent atrial fibrillation	1.53 (0.85, 2.74)	0.15		
Hypertension	0.77 (0.47, 1.24)	0.27		
Diabetes mellitus	0.96 (0.71, 1.29)	0.77		
Dyslipidemia	1.01 (0.58, 1.78)	0.97		
Prior history of myocardial infarction	1.39 (0.50, 3.86)	0.53		
Prior history of HF	1.43 (1.04, 1.98)	<0.05		
Chronic kidney disease	1.02 (0.84, 1.24)	0.83		
Echocardiographic				
LV end-diastolic dimension (per 1 mm)	1.04 (0.98, 1.10)	0.20		
LV end-systolic dimension (per 1 mm)	1.08 (1.03, 1.13)	<0.01		
LV ejection fraction (per 10%)	0.66 (0.50, 0.86)	<0.01	0.67 (0.52, 0.86)	<0.01
LV end-diastolic septal wall thickness (per 1 mm)	1.27 (1.11, 1.46)	<0.001		
LV end-diastolic posterior wall thickness (per 1 mm)	1.19 (1.03, 1.38)	<0.05		
Indexed LV mass (per 10 g/m^2)	1.18 (1.09, 1.28)	<0.0001	1.13 (1.03, 1.24)	<0.05
LA dimension (per 1 mm)	1.02 (0.99, 1.06)	0.15		
LA volume (per 10 ml)	1.10 (1.06, 1.14)	<0.0001		
Indexed LA volume (per 10 ml/m^2)	1.16 (1.09, 1.23)	<0.0001	1.14 (1.06, 1.22)	<0.001
Mitral inflow Doppler induces				
E (per 10 cm/s)	0.98 (0.86, 1.10)	0.69		
E deceleration time (per 10 ms)	0.99 (0.95, 1.04)	0.66		
Tissue Doppler imaging				
E' (per 1 cm/s)	0.88 (0.77, 1.02)	0.08		
E/E'	1.02 (0.95, 1.09)	0.64		

CI = confident interval, HF = heart failure, HR = hazard ratio, LA = left atrial, LV = left ventricular.

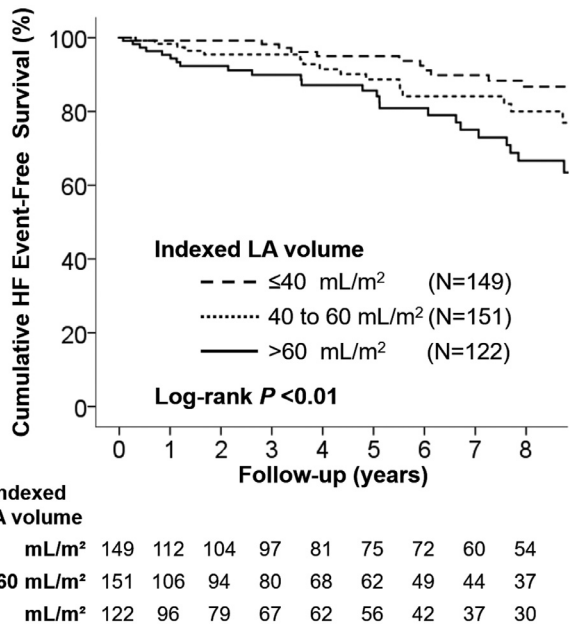
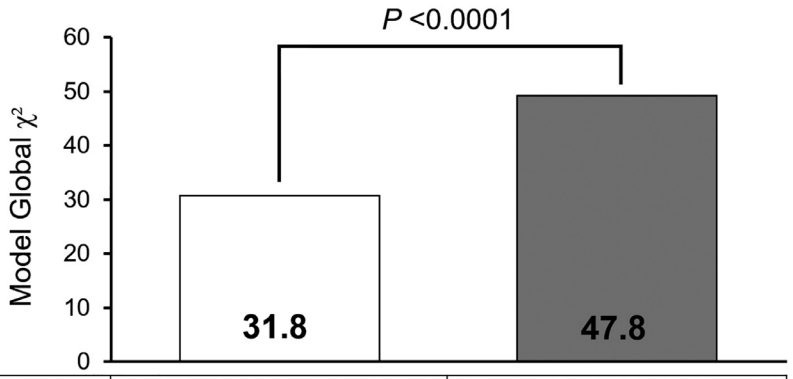


Figure 1. The Kaplan-Meier estimates of cumulative heart failure (HF) event-free survival stratified by indexed left atrial (LA) volume category (indexed LA volume ≤40 ml/m^2, 40 to 60 ml/m^2, >60 ml/m^2).

emerging evidence.[2,6,7] However, despite the advances in the management of AF, the incidence and mortality risk of HF after diagnosis of AF has not been reduced in the past 2 decades.[2,4] Furthermore, the prevalence of AF and HF increases dramatically with advancing age, and the number of patients with both AF and HF is expected to increase in the coming decades as the population ages, presenting a growing clinical and economic burden.[5,14–16] Therefore, prediction of HF development in patients with AF is important for risk stratification in clinical practice.

In patients with sinus rhythm, it has been well known that LA volume measured by 2-dimensional echocardiography is a robust predictor of HF development.[1,8,9,17] During ventricular diastole, the left atrium is directly exposed to LV pressure through the open mitral valve. Thus, LA size has been demonstrated as a marker of elevated LV filling pressure as well as the severity and chronicity of LV diastolic dysfunction in patients without mitral valve disease or left-to-right shunts.[18–21] However, among patients with AF, the clinical utility of LA volume as a prognostic implication of HF development has not been fully established.

Our study showed that indexed LA volume was a strong predictor of HF development, independently of other conventional risk factors in patients with AF. Previously, Tsang et al reported that LA volume was shown as a significant predictor of cardiovascular events in patients with sinus



	Age + LV ejection fraction + Indexed LV mass	Age + LV ejection fraction + Indexed LV mass + Indexed LA volume
Age	1.79 (1.23, 2.61), *P* <0.01	1.71 (1.16, 2.52), *P* <0.01
LV ejection fraction	0.68 (0.53, 0.88), *P* <0.01	0.67 (0.52, 0.86), *P* <0.01
Indexed LV mass	1.18 (1.08, 1.28), *P* <0.001	1.13 (1.03, 1.24), *P* <0.05
Indexed LA volume		1.14 (1.06 1.22), *P* <0.001

Figure 2. The predictive power of 2 models for heart failure development. The global log likelihood ratio chi-square of sequential Cox models incorporating risk factors including age, left ventricular (LV) ejection fraction indexed left ventricular mass, and indexed left atrial (LA) volume were illustrated.

rhythm, but not in patients with AF, which is inconsistent with our study findings.[1] The possible reasons for the difference relate to differences in the number of study patients, duration of follow-up period, and the outcome of interests. In the study by Tsang et al, the outcome of interests was a combination of "cardiovascular events" including stroke, transient ischemic attack, myocardial infarction, coronary revascularization, and cardiovascular death. In contrast, we investigated new HF events as an outcome. In the study by Tsang et al, the number of study patients in AF subgroup consisted of only 106 patients, and 35 patients had 43 new "cardiovascular events" during a mean follow-up period of 3.0 ± 2.4 years, whereas study patients in our study consisted of 422 patients, and 52 patients had new HF events during a mean follow-up period of 4.6 ± 3.6 years. In a recent study by Potpara et al, large anteroposterior LA dimension (>40 mm) was shown to be a risk of incident HF among patients with AF and preserved LV ejection fraction.[22] Although they did not assess the LA volume, this findings is supportive of our results. It is well known that LA volume represented a superior measure for LA size over LA dimension.[9,23] In this AF cohort study, LA volume provides superior prognostic information for the prediction of HF development compared with LA dimension.

It is well known that increased LV filling pressure and LV diastolic dysfunction, which results in mechanical stretch of the LA wall, play an important role in the development of AF as well as LA remodeling and HF development.[9,21,24] Indeed, it is demonstrated that LA volume in patients with AF is larger than that in patients with sinus rhythm.[1,25,26] In the present study, indexed LA volume (52.3 ± 27.4 ml/m^2) were larger than the previously reported values in sinus rhythm population-based study,[8,27] and were similar to that in AF population-based study.[26,28] It has also been reported that AF itself causes atrial as well as ventricular myocardial fibrosis, which leads to further LA structural remodeling or HF development.[5,29] Considering these facts, the degree of LA enlargement may be related to the susceptibility to HF development, and it is not surprising that the increment of LA volume category was shown to be associated with increased risk of developing HF in this study. Thus, the patients with a combination of AF and large LA size need careful follow-up in clinical practice.

We acknowledge the limitation of this study. Because of the study design, data with respect to the medical therapy before HF events were not readily available, and how these factored into the development of the events is not known. It is possible that silent AF may not have been included, and data on duration of AF history is not considered. We do not have initial hemodynamic data available, and thus, we could not reveal the underlying mechanism of LA enlargement in patients with AF. Finally, because of the study patients were referral based, and the number of study patients is relatively small, the extent to which the findings can be generalized to other population groups needs to be verified in future studies.

In conclusion, in patients with AF, LA volume provides prognostic information for the prediction of new HF events, and is useful for identifying patients at risk of future HF development. Whether effective treatment to decrease LA volume translates to the improvement in outcomes requires further investigations.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.049.

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