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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Clinical, Electrocardiographic, and Echocardiographic Parameter Combination Predicts the Onset of Atrial Fibrillation

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Background: The ability to identify risk markers for new-onset atrial fibrillation (AF) is critical to the development of preventive strategies, but it remains unknown whether a combination of clinical, electrocardiographic, and echocardiographic parameters predicts the onset of AF. In the present study, we evaluated the predictive value of a combined score that includes these parameters.

Methods and Results: We retrospectively studied 1,040 patients without AF who underwent both echocardiography and 24-h Holter electrocardiography between May 2005 and December 2010. During a median follow-up period of 68.4 months (IQR, 49.9–93.3 months), we investigated the incidence of new-onset AF. Of the 1,040 patients, 103 (9.9%) developed AF. Patients who developed AF were older than patients who did not. Total heart beats, premature atrial contraction (PAC) count, maximum RR interval, and frequency of sinus pause quantified on 24-h electrocardiography were associated with new-onset AF. LA diameter (LAD) on echocardiography was also associated with the development of AF. On multivariate Cox analysis, age ≥58 years, PAC count ≥80 beats/day, maximum RR interval ≥1.64 s, and LAD ≥4.5 cm were independently associated with the development of AF. The incidence rate of new-onset AF significantly increased as the combined score (i.e., the sum of the risk score determined using hazard ratios) increased.

Conclusions: A combined score that includes age, PAC count, maximum RR interval, and LAD could help characterize the risk of new-onset AF.

Key Words: Atrial fibrillation; Left atrial diameter; Premature atrial contraction

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders. Its prevalence is expected to rise dramatically as the population ages. AF is associated with increased mortality and morbidity, including cardiac dysfunction and thromboembolic events.[1] Although prompt management of AF may reduce the incidence of these complications, AF is often not diagnosed until severe complications occur. Therefore, the ability to identify risk markers for the first episode of AF is critical to the development of preventive strategies. Advanced age, diabetes, hypertension, and cardiovascular disease, such as coronary artery disease (CAD) and valvular heart disease, have been shown to increase the risk of developing AF.[2,3] Echocardiographic left atrial (LA) size[3–5] and diastolic dysfunction[5,6] have also been shown to predict the onset of AF. Furthermore, the addition of premature atrial contraction (PAC) count to a validated AF risk algorithm provides superior AF risk discrimination.[7–9] It remains unknown, however, whether a combination of clinical, electrocardiographic, and echocardiographic parameters can predict the onset of AF. In the present study, we evaluated the predictive value of a combined score that includes these parameters.

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Table 1. Subject Characteristics vs. AF Status

	No AF (n=937)	New-onset AF (n=103)	P-value
Age (years)	61±14	67±10	<0.001
Male (%)	480 (51.2)	61 (59.2)	0.123
BMI (kg/m^2)	23.6±4.2	23.6±3.8	0.981
Hypertension	567 (60.5)	71 (68.9)	0.096
Dyslipidemia	429 (45.8)	53 (51.5)	0.273
Diabetes mellitus	311 (33.2)	33 (32.0)	0.814
CAD	400 (42.7)	43 (41.7)	0.854
Non-rheumatic valvular disease	192 (20.5)	17 (16.5)	0.338
Cardiomyopathy	124 (13.2)	16 (15.5)	0.516
CHF	12 (1.3)	2 (1.9)	0.581
COPD	10 (1.1)	3 (2.9)	0.110

Data given as mean±SD or n (%). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congenital heart disease; COPD, chronic obstructive pulmonary disease.

Methods

Patients

We retrospectively studied 1,176 consecutive patients with palpitation, chest pain, dizziness, or syncope in whom both echocardiography and 24-h Holter electrocardiography were performed between May 2005 and December 2010 and could be followed thereafter at Tokushima University Hospital. Patients were excluded if they had previously documented AF or AF diagnosed based on 24-h Holter electrocardiography. Patients with rheumatic heart disease, unstable angina, decompensated congestive heart failure, hyperthyroidism, and pacemakers or implantable cardioverter defibrillators were also excluded from the present study. The final analysis involved 1,040 patients.

Holter Electrocardiography

Baseline 24-h Holter electrocardiography (Cardiomemory RAC-3103, Nihon Kohden, Tokyo, Japan) was interpreted by 2 independent cardiologists. The following variables were measured for each group: total (overall) heart beats; maximum RR interval; presence of sinus pause (defined as >2 s); and the total number of PAC and premature ventricular contraction (PVC) episodes. In addition, the maximum continuous PAC count was also evaluated.

Echocardiography

Transthoracic echocardiography was performed by experienced sonographers ≤1 month of Holter electrocardiography using a commercially available ultrasound machine (Vivid 9, GE Vingmed, Horten, Norway or iE33, Philips, Andover, MA, USA). Baseline echocardiography included standard 2-D measurements of left ventricular (LV) end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV end-diastolic dimension (LVDd), LV end-systolic dimension (LVDs), interventricular septal thickness (IVS), LV posterior wall thickness (LVPW), and LA dimension (LAD). LV ejection fraction (LVEF) was calculated by dividing the difference between LVEDV and LVESV by LVEDV. Fractional shortening (FS) was also calculated as (LVDd−LVDs)/LVDd. LV mass was calculated using the following formula: LV mass=$1.05\times[(LVDd+LVPW+IVS)^3-LVDd^3]-13.6$, and normalized for body surface area to obtain the LV mass index (LVMI).

Using pulsed-wave Doppler echocardiography, the transmitral flow velocity profile was recorded in the apical 4-chamber view or the apical long-axis view with the sample volume positioned at the level of the mitral valve tips during diastole. The early (E) and atrial (A) velocities were measured. The tricuspid regurgitation pressure gradient (TRPG) was also measured.

Follow-up

During the follow-up period, we investigated the incidence of new-onset AF. Data on new occurrences of AF in the follow-up period were retrieved from the hospital medical records and discharge summaries as well as from other institutions.

Statistical Analysis

Results are expressed as mean±SD for normally distributed variables or median (IQR) for non-normally distributed variables. Means or proportions of clinical characteristics and measured risk factors were compared between patients with and without new-onset AF using Student's t-test or chi-squared test. From this analysis, potential predictors of new-onset AF were identified, and variables with $P<0.05$ were entered into the univariate Cox proportional hazards models to estimate the contribution of various risk factors to the prediction of new-onset AF during the follow-up period. This set of variables was reduced by forward stepwise algorithm until only those significant at $P<0.05$ remained in the multivariate model. In the Cox models, for continuous independent variables, receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-offs of continuous variables. Optimal cut-off points were obtained for each marker using Youden index. Kaplan-Meier curves for freedom from AF events were calculated to describe the occurrence of new AF events by risk factor based on the best cut-off on ROC curve analysis. Risk scores for new-onset AF were developed based on Cox proportional hazards analysis. A combined score for AF prediction was calculated as the sum of the risk scores. Differences between high and low levels of these factors were tested using log-rank test. $P<0.05$ was considered statistically significant.

Table 2. Holter Electrocardiography vs. AF Status

	No AF	New-onset AF	P-value
Total heart beats (beats/24 h)	101,974±16,334	96,299±14,085	0.001
PVC count (beats/24 h)	10 (2–224)	20 (2–275)	0.827
PAC count (beats/24 h)	39 (11–146.5)	204 (38–1,508)	0.021
Maximum no. continuous PAC (beats)	2 (0–5)	5 (2–9)	0.051
Sinus pause (/24 h)	0 (0–0) (17.5±167.9)	0 (0–0) (142.9±1,169.0)	0.003
Maximum RR interval (ms)	1,496 (1,320–1,712)	1,680 (1,440–1,832)	<0.001

Data given as mean±SD or median (IQR). AF, atrial fibrillation; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Table 3. Echocardiography vs. AF Status

	No AF	New-onset AF	P-value
LAD (cm)	3.78±0.65	4.06±0.76	<0.001
LVDd (cm)	4.82±0.71	4.83±0.74	0.985
LVDs (cm)	3.08±0.78	3.08±0.76	0.975
FS (%)	36.7±8.3	36.7±8.0	0.998
IVS (mm)	9.8±3.6	10.2±2.9	0.311
LVPW (mm)	9.6±3.3	9.6±1.9	0.818
LVMI (g/m^2)	120.5±45.4	123.5±38.2	0.568
LVEDV (mL)	89.7±35.9	93.5±34.6	0.379
LVESV (mL)	35.3±26.8	34.4±22.2	0.800
LVEF (%)	63.0±11.3	64.4±11.2	0.308
Transaortic flow (m/s)	0.97±0.36	0.96±0.32	0.810
E wave (cm/s)	63.7±21.1	68.0±24.7	0.075
A wave (cm/s)	72.0±21.2	71.0±23.7	0.669
E/A	0.97±0.51	1.02±0.61	0.369
TRPG (mmHg)	21.5±8.4	22.7±7.0	0.352

Data given as mean±SD. AF, atrial fibrillation; FS, fractional shortening; IVS, interventricular septum thickness; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall thickness; TRPG, tricuspid regurgitation pressure gradient.

Table 4. Independent Indicators of New-Onset AF

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥58 years)	3.522	1.968–6.302	<0.001	1.868	1.008–3.464	0.047
PAC count (≥80 beats)	4.164	2.751–6.303	<0.001	3.077	1.956–4.841	<0.001
Maximum RR interval (≥1.64 s)	2.628	1.777–3.887	<0.001	1.704	1.131–2.569	0.011
LAD (≥4.5 cm)	2.853	1.818–4.477	<0.001	1.839	1.155–2.927	0.010
Total heart beats (≥101,600 beats)	2.155	1.418–3.271	<0.001			
Sinus pause (≥36/24 h)	4.215	2.194–8.099	<0.001			

AF, atrial fibrillation; LAD, left atrial diameter; PAC, premature atrial contraction.

Results

A total of 1,040 patients (mean age, 62±14 years; 52.0% men) were included in the present study. During the median follow-up period of 68.4 months (IQR, 49.9–93.3 months), new-onset AF occurred in 103 patients (9.9%) with an incidence of 17.0 cases of AF per 1,000 person-years.

Clinical Characteristics

Table 1 summarizes the patient clinical characteristics according to new-onset AF status. Patients who developed AF were older than patients who did not. There were no significant differences in gender, body mass index (BMI), or prevalence of hypertension, dyslipidemia, diabetes mellitus, and CAD.

Baseline Characteristics

Holter Electrocardiography Total heart beats was lower and maximum RR interval was longer in patients with new-onset AF than in those without (**Table 2**). In addition, sinus pauses and PAC occurred more frequently in patients with AF than in those without. In contrast, there were no significant differences in PVC count or in the maximum number of continuous PAC.

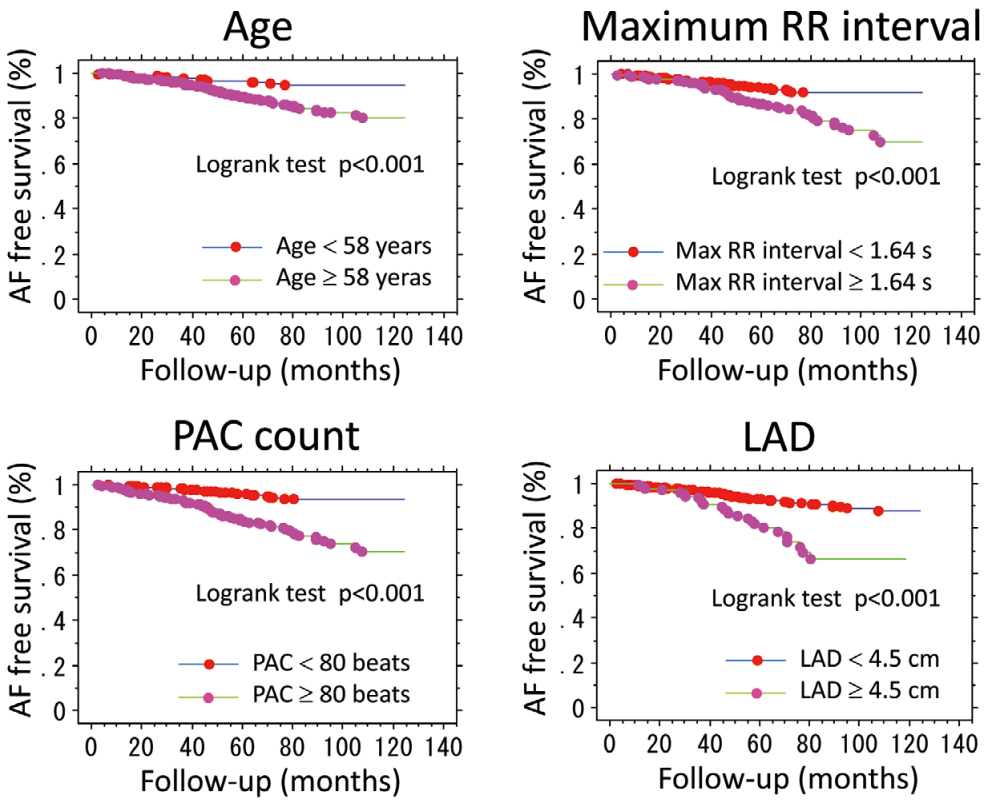

Figure 1. Kaplan-Meier estimates of survival free from new-onset atrial fibrillation (AF) according to age (≥58 years), sinus pauses (≥1.64 s), frequent premature atrial contraction (PAC; ≥80 beats/day), and left atrial diameter (LAD; ≥4.5 cm).

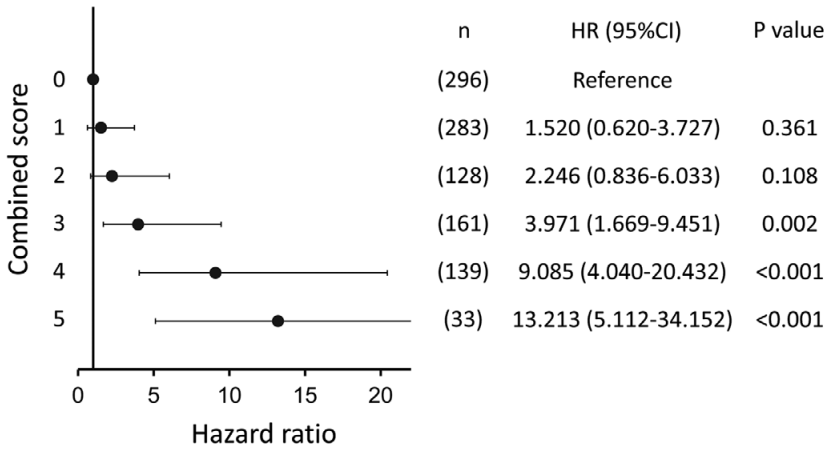

Figure 2. Hazard ratio for new-onset atrial fibrillation (AF) according to the combined score.

Echocardiography LAD was larger in patients with new-onset AF than in those without, but there were no significant differences in LVDd, LVDs, FS, IVS, LVPW, LVMI, LVEDV, LVESV, LVEF, trans-aortic flow, E wave, A wave, E/A ratio, or TRPG (**Table 3**).

Prediction of New-Onset AF

The variables with P<0.05 according to new-onset AF status in **Tables 1**–**3** were entered into the univariate Cox proportional hazards models (**Table 4**). For the Cox proportional analysis and Kaplan-Meier curves for freedom from AF, the cut-offs of the possible risk factors were determined on ROC curve analysis. Total heart beats and sinus pause, which had collinearity with maximum RR interval, were excluded from the multivariate analysis based on stepwise selection. On multivariate Cox analysis,

age, PAC count, maximum RR interval, and LAD were independently associated with the development of AF (multivariable-adjusted hazard ratios [HR]: age ≥58 years, 1.868; PAC count ≥80 beats/day, 3.077; maximum RR interval ≥1.64 s, 1.704; and LAD ≥4.5 cm, 1.839; **Table 4**). On Kaplan-Meier analysis for freedom from AF, the risk of a new occurrence of AF was higher in patients with advanced age (≥58 years), frequent PAC (≥80 beats/day), longer maximum RR interval (≥1.64 s), and longer LAD (≥4.5 cm) than in those without (**Figure 1**). Therefore, the combined score for AF prediction was calculated as the sum of the weighted scores (age ≥58 years, 1; PAC ≥80 beats/day, 2; maximum RR interval ≥1.64 s, 1; LAD ≥4.5 cm, 1) derived from the Cox proportional HR. The HR for a combined score of 3, 4, or 5 for new-onset AF were significantly increased (combined score 3, HR, 3.971; 95% CI: 1.669–9.451, P=0.002; score 4, HR, 9.085; 95% CI: 4.040–20.432, P<0.001; and score 5, HR, 13.213; 95% CI: 5.112–34.152, P<0.001) compared with a score of 0 (HR, 1; **Figure 2**). Based on the combined score, the patients were stratified into 3 risk groups for new-onset AF (scores 0–1; 2–3; and 4–5). On Kaplan-Meier curve analysis, the incidence rate of new-onset AF significantly increased as the combined score increased (**Figure 3**). The area under the curve (AUC) of the combined score based on these 4 parameters was 0.74.

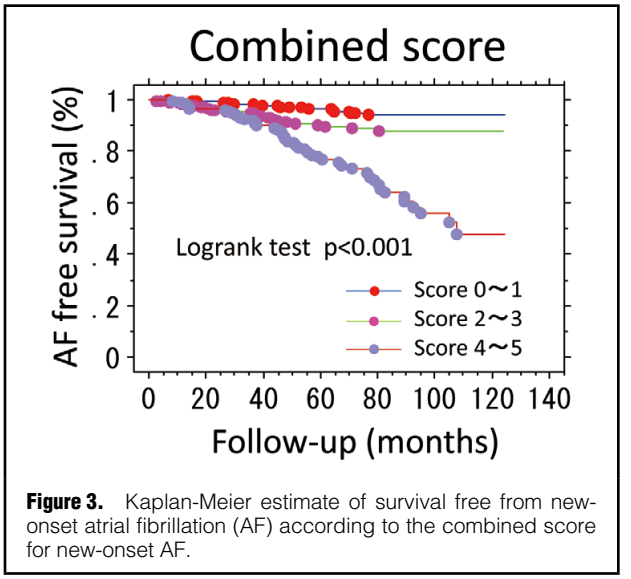

Figure 3. Kaplan-Meier estimate of survival free from new-onset atrial fibrillation (AF) according to the combined score for new-onset AF.

Discussion

The present study has shown that age, PAC count, maximum RR interval, and LAD were independently associated with increased risk of future AF, and, furthermore, that a combined score involving these 4 parameters might be more useful for predicting new-onset AF.

Advanced age had the highest clinical predictive value for new-onset AF in the present study, which is consistent with previous studies.[2,3] In contrast, other clinical characteristics including hypertension, diabetes, and CAD were not associated with the development of AF in the present study. The small sample size and heterogeneity in the duration of illness and treatment might explain discrepancies between previous studies and the present one. In the present study, BMI was also not associated with new-onset AF, although previous studies in Western countries suggest that obesity is associated with an increased risk of AF.[10,11] This discrepancy might be due to the lower prevalence of apparent obesity in the present Japanese sample (mean BMI, 23.6 kg/m^2) than in previous Western studies (mean BMI, ≥26 kg/m^2).

In the present study, of the Holter electrocardiographic parameters, PAC count as well as total heart beats, maximum RR interval, and frequency of sinus pauses were associated with new-onset AF. PAC count has been shown to provide superior AF risk discrimination,[7–9] supporting the present results. The most plausible mechanism is that PAC from the pulmonary veins trigger AF.[12] In addition, a higher number of PAC might be an early manifestation of hypertension or of underlying structural heart disease that elevates filling pressures. There might also be a possible link between sinus node dysfunction and AF.[13–15] The potential mechanisms of the relationship between sinus node dysfunction and AF are structural, electrical, and autonomic remodeling based on renin-angiotensin system activation, malfunction of ion channels or gap junctions, and mutations in the emerin gene.[15] To the best of our knowledge, however, no previous studies have demonstrated the predictive value of parameters related to sinus node dysfunction for new-onset AF. Interestingly, in the present study, reduced total heart beats, longer maximum RR interval, and frequent sinus pauses predicted new-onset AF. Given that occult AF might induce sinus node dysfunction, further detailed studies are needed.

In the present study, the only echocardiographic parameter associated with new-onset AF was LAD. This is in agreement with previous studies demonstrating that echocardiographic parameters including enlarged LAD, increased LV wall thickness, and reduced LV systolic function predicts the risk of non-rheumatic AF. In contrast, LA size was found to have increased after the onset of AF in some follow-up studies.[16,17] Evidence that increased LA size precedes the development of AF, however, does not necessarily imply causality. LA enlargement might simply be an alternative marker of unidentified factors that are causally related to the development of AF. For instance, hypertension or hypertensive heart disease have been shown to contribute to the development of LA enlargement.[18] In contrast, normal aging by itself does not contribute to LA enlargement.[19] In the present study, echocardiographic parameters besides LAD, including FS, LVMI, LVEDV, LVEF, and E/A ratio, were not associated with new-onset AF, which is not compatible with previous studies.[3–6] Given that exclusion criteria for the present study included decompensated congestive heart failure, rheumatic heart disease, and unstable angina; almost all patients had normal systolic function without structural heart disease. These patient characteristics might lead to discrepancies between the present study and previous ones.

In the present study, we created a combined score for AF prediction calculated as the sum of weighted scores (age ≥58 years, 1; PAC ≥80 beats/day, 2; maximum RR interval ≥1.64 s, 1; LAD ≥4.5 cm, 1). Interestingly, the HR for new-onset AF with a combined score of 3, 4, and 5 were markedly increased compared to the score 0. This is in agreement with the present finding that these 4 parameters are independently associated with the development of AF. To the best of our knowledge, there have been no

previous studies evaluating the predictive power of a combination of clinical, electrocardiographic, and echocardiographic parameters for AF onset, although some studies have suggested the usefulness of a combination of clinical and electrocardiographic parameters[9] or clinical and echocardiographic parameters[20] or clinical, laboratory, and echocardiographic parameters.[21]

The present AUC for the combined score (0.74) was similar to that of previous risk scores in the Framingham Heart Study (AUC, 0.78)[20] and the CHART-2 Study (AUC, 0.76).[21] Although these previous scores have a high AUC, they include more parameters than those in the present study and are very complex for clinical use. In addition, the CHART-2 Study included Japanese patients at higher risk of heart failure compared with the present subjects. Given that the present parameters can be easily evaluated in any clinic or hospital, this combined score, which includes fewer parameters, may be easily applied to the clinical setting. Furthermore, early identification of patients at risk of AF may enable more timely intervention, thereby preventing complications including ischemic stroke.

Interestingly, in the present study, Kaplan-Meier estimates for AF prediction based on the combined score or on each parameter showed that difference in AF onset increased after 50–60 months of follow-up. This suggests that the combined score predicts AF onset after ≥4–5 years. In the Framingham Heart Study (a community-based cohort study), the assessment of AF risk score was based on a maximum follow-up of 10 years.[20] In contrast, in the CHART-2 Study, new-onset AF was assessed during a median 3.2-year follow-up in patients with overt chronic heart failure.[21] Compared with these 2 studies, the present study assessed new AF onset in intermediate-risk patients without decompensated congestive heart failure during an intermediate median follow-up period of 68.4 months.

The present study has several limitations. First, this study was retrospective and the number of patients was relatively small. A prospective study with more patients is necessary to define the clinical implications. Second, the incidence of transient AF may have been underestimated because some asymptomatic patients may have not been diagnosed with AF. Third, the combined score may predict AF onset after ≥4–5 years and may not in a few years. Fourth, we used LAD but not LA volume as the parameter of LA size because we did not measure LA volume routinely in all patients with echocardiography during the data collection period. LAD, however, may be more straightforward and easily applicable than LA volume in the clinical setting.

In conclusion, a combined score incorporating age, PAC count, maximum RR interval, and LAD can help characterize the risk of new-onset AF.

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Disclosures

The authors declare no conflicts of interest.

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