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Real-Time Pathophysiologic Correlates of Left Atrial Appendage Thrombus in Patients Who Underwent Transesophageal-Guided Electrical Cardioversion for Atrial Fibrillation

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Abstract

Although current guidelines advocate using the CHA_2DS_2-VASc score to assess the risk of stroke in patients with atrial fibrillation (AF), compared with transesophageal echocardiography (TEE), its ability to predict left atrial appendage thrombus (LAAT) is limited. We studied 3,324 consecutive patients with sustained AF from our prospective registry of patients who underwent first-time TEE-guided electrical cardioversion (ECV) from May 2000 through March 2012. The association of CHA_2DS_2-VASc score or TEE risk factors with the occurrence of LAAT was analyzed. The mean (SD) age was 69 (12.5) years and 67% were men. LAAT was identified in 49 (1.5%) during pre-ECV TEE. Compared with patients without LAAT, those with LAAT had lower peak left atrial appendage emptying velocity (LAAEV) (17.2 ± 8.5 vs 36.6 ± 20.8; p <0.001) and left ventricular ejection fraction (LVEF) (39.9 ± 17.6 vs 51.4 ± 13.7; p <0.001); their CHA_2DS_2-VASc score also was higher, but the difference was not statistically significant (3.6 ± 1.4 vs 3.2 ± 1.6; p = 0.06). Multivariate logistic regression analysis identified an LVEF ≤40% (adjusted odds ratio 2.48, 95% confidence interval 1.38 to 4.46), LAAEV 20.3 to 33.9 cm/s (odds ratio 12.19, 95% confidence interval 1.53 to 96.86), and LAAEV ≤20.2 cm/s as independent predictors of LAAT. An LAAEV cut-point of 20 cm/s and an LVEF ≤40% were optimal for detecting LAAT (sensitivity 75% and 62%; specificity 77% and 75%; area under the curve 0.822 and 0.776, respectively). On follow-up, LAAT was an independent risk factor of subsequent ischemic stroke but did not influence survival. In conclusion, reduced LVEF and reduced LAAEV are important pathophysiologic correlates of left atrial appendage thrombogenesis and subsequent ischemic stroke in patients who underwent TEE-guided ECV for AF.

Atrial fibrillation (AF) is a major public health problem in the developed world,[1] and is associated with an increased risk of stroke,[2] generally attributed to the formation of left atrial appendage thrombus (LAAT) and distal embolization.[3] Current guidelines advocate using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes

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Disclosures

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mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, gender category) score for estimation of stroke risk in patients with AF.[4] However, the discriminatory ability of the CHA_2DS_2-VASc score for predicting LAAT is modest with a c-statistic of 0.607.[5] The role of transesophageal echocardiography (TEE) for the assessment of LAAT is well-established.[6] We have demonstrated an independent association between TEE-measured left atrial appendage (LAA) emptying velocity (LAAEV) and subsequent ischemic stroke after successful electrical cardioversion (ECV) of AF.[7] In this investigation, we sought to determine the ability of TEE risk factors, principally correlates of systolic (left ventricular ejection fraction [LVEF]) and diastolic (LAAEV) dysfunction,[8] compared with the CHA_2DS_2-VASc score to predict LAAT before ECV for AF.

Methods

The study protocol was approved by the Mayo Clinic Institutional Review Board. We prospectively collected data from consecutive eligible patients with sustained AF who underwent TEE to exclude LAAT before restoration of sinus rhythm by ECV from May 2000 through March 2012. Sustained AF was defined as AF that fails to self-terminate. LAAT was defined echocardiographically as a well-circumscribed, often mobile, highly reflective mass of uniform consistency, with texture different from the atrial wall and with a border distinct from the surrounding structures in multiple imaging planes.[9] We identified 3,340 consecutive patients with sustained AF who underwent first-time TEE-guided ECV during the study period. We excluded patients with history of complex congenital heart disease or LAA closure (n = 16), yielding a total of 3,324 patients.

The precardioversion TEE protocol has been described previously.[7,10,11] Briefly, all patients underwent TEE immediately before ECV. Echocardiographic data, including LVEF and LAAEV, were routinely assessed. The peak LAAEV profiles were measured over 5 consecutive cardiac cycles using pulsed-wave Doppler interrogation with the sample volume positioned 1 cm within the orifice of the LAA. In the absence of an intracardiac thrombus, ECV was performed using established monophasic (2000) or biphasic (2001 to 2012) waveform protocols of the cardioversion unit for cardioversion of AF.[12]

The primary outcome of the study was LAAT, which was determined by TEE immediately before ECV. The secondary outcomes were first documented ischemic stroke and all-cause mortality. Stroke was defined as the acute onset focal neurologic deficits persisting more than 24 hours, and based on results of CT or MRI or autopsy (if available). Vital status was ascertained through 2014 by using the National Death Index.

Categorical variables were expressed as counts and percentages and compared by chi-square analysis or Fisher's exact test, depending on the distribution of the data. Continuous variables were expressed as means (SD) or median and interquartile ranges. Variables were compared by using the Student's *t* test or the Wilcoxon rank-sum test. Predictors of LAAT were assessed with a multivariable logistic regression analysis. The measurement of predictive accuracy of the echocardiographic parameters (e.g., LAAEV, LVEF) in screening for LAAT was assessed by using a receiver operating characteristic curve. Cox regression models were used to identify potential factors associated with ischemic stroke or with all-

cause mortality. Results of these analyses were expressed as hazard ratios and 95% confidence intervals. Multicollinearity was examined by using a correlation matrix and diagnostic statistics. Survival-free estimates of neurologic events and death were computed by using the Kaplan-Meier method and compared with a log-rank test. A 2-tailed p value of <.05 was considered significant. All statistical analyses were performed by using the SAS version 9.4M3 (SAS Institute Inc., Cary, North Carolina) and R v3.1 (R Development Core Team, 2016, Vienna, Austria).

Results

Baseline characteristics and demographics of the study patients are listed in Table 1. The mean (SD) age was 69 (12.5) years and 67% were men. Overall, 71% of patients were receiving oral anticoagulation (OAC) therapy with warfarin or a novel oral anticoagulant at the time of TEE. LAAT was identified in 49 patients (1.5%) during precardioversion TEE. Compared with patients without LAAT, those with LAAT had lower mean (SD) LAAEV (17.2 [8.5] vs 36.3 [20.8] cm/s; p <0.001) and LVEF (39.9% [17.6%] vs 51.4% [13.7%]; p <0.001) and a higher nonsignificant mean (SD) CHA_2DS_2-VASc score (3.6 [1.4] vs 3.2 [1.6]; p = 0.06).

We performed a univariate logistic regression analysis to identify associations between precardioversion clinical and echocardiographic features with LAAT (Table 2). Candidate variables (characteristics with a p value <0.10) were entered into stepwise multivariable logistic regression models. This analysis identified moderately reduced peak LAAEV (20.3 to 33.9 cm/s) (odds ratio [OR] 12.19, 95% confidence interval [CI] 1.53 to 96.86), severely reduced LAAEV ≤20.2 cm/s (OR 65.85, 95% CI 8.93 to 485.39), and moderately reduced or lower LVEF (defined as ejection fraction ≤40%) (OR 2.48, 95% CI 1.38 to 4.46) as independent predictors of LAAT (c-statistic, 0.849) (Table 3A). When CHA_2DS_2-VASc components were included in lieu of CHA_2DS_2-VASc score, results were similar; LVEF ≤40% or CHF and reduced LAAEV remained significant predictors of LAAT (Table 3B).

During a mean (SD) follow-up of 4.8 (3.6) years, 182 ischemic strokes occurred. The cumulative stroke-free survival in the entire population is shown in Figure 1. By Kaplan-Meier analysis, the stroke-free survival rate was significantly lower for patients with LAAT compared with those without LAAT (log-rank test, p = 0.006). Results of univariate Cox regression analysis are listed in Table 2. In multivariable Cox regression analysis, LAAT (hazard ratio [HR] 2.84, 95% CI 1.30 to 6.19), CHA_2DS_2-VASc score >2 (HR 4.35, 95% CI 1.38 to 13.76]), and severely reduced LAAEV ≤20.2 cm/s (HR 1.46, 95% CI 1.03 to 2.07) emerged as independent predictors of ischemic stroke (c-statistic, 0.726).

Of the 3,324 patients in the study, 1,118 (33.6%) died during follow-up. The cumulative survival of the entire cohort is illustrated in Figure 2. By Kaplan-Meier analysis, cumulative survival rates were not significantly different between patients with and without LAAT (p = 0.81). Multivariable Cox proportional hazards regression analysis (Table 3) showed that a CHA_2DS_2-VASc score of 1 (HR 2.03, 95% CI 1.16 to 3.57), CHA_2DS_2-VASc score of 2 (HR 2.32, 95% CI 1.38 to 3.92), CHA_2DS_2-VASc score >2 (HR 4.96, 95% CI 3.02 to 8.15), LAAEV ≤20.3 to 33.9 cm/s (HR 1.21, 95% CI 1.04 to 1.39), and LAAEV ≤20.2 cm/s (HR

1.39, 95% CI 1.19 to 1.62) were independent predictors of all-cause mortality (c-statistic, 0.859).

Receiver operating characteristic curve analysis showed good discriminatory capacity of LAAEV and fair for LVEF in predicting LAAT in patients with AF who underwent TEE-guided ECV. An LAAEV cut-point of 20.2 cm/s was optimal for detecting LAAT (sensitivity, 75%; specificity, 77%; area under the curve [AUC], 0.822) (Figure 3). An LVEF cut-point of 40% was also useful for detecting LAAT (sensitivity, 62%; specificity, 75%; AUC, 0.776) (Figure 3).

Discussion

In this large cohort of patients who underwent TEE-guided ECV for AF, the prevalence of LAAT among patients who underwent TEE was 1.5%. LAAT was strongly associated with reduced LVEF and reduced peak LAAEV, independent of other clinical and echocardiographic risk factors. A LAAEV cut-point of 20.2 cm/s and a LVEF cut-point of 40% provided optimal sensitivity and specificity for detecting LAAT. Reduced LAAEV, LAAT, and CHA_2DS_2-VASc score >2 were independent predictors of subsequent stroke. These results provide additional evidence that LVEF and LAAEV are not just pathophysiologic echocardiographic correlates of systolic and diastolic dysfunction[8]; rather, they may be considered surrogate markers of LAAT and subsequent ischemic stroke in patients who underwent TEE-guided ECV for AF.

Although LAAT is recognized as a major cause of stroke and thromboembolism in patients with AF,[13] its true prevalence remains unknown. Previous studies have shown wide variation in diagnostic yield of TEE for LAAT in patients with AF, ranging from 0.5% to 15%.[14–17] A recent meta-analysis that examined 20,516 patients with AF who underwent TEE from 72 studies reported a prevalence of LAAT of 9.8%.[18] In contrast, Puwanant et al[17] reviewed more than 1,000 preablation TEEs and reported that LAAT was present in 0.6% of patients with AF. Although the low prevalence of LAAT (1.5%) in our study was consistent with other studies of patients with AF who underwent preprocedural TEE,[16,17] it contrasts with previous observations of patients with AF who underwent TEE generally for the detection of LAAT.[6,19] This difference in prevalence rates of LAAT could be due to heterogeneity among the studies, level of oral OAC, and technological improvement in echocardiography over time. Although TEE screening for LAAT before cardioversion is recommended for patients with AF lasting ≥48 hours (or of unknown duration) who have not received OAC for at least 3 weeks,[4] definitive evidence-based data for this recommendation are lacking. Previous studies have demonstrated that thrombus formation in the LAA has a dominant role in the thromboembolic risk associated with AF.[3,20] Consistent with previous reports,[13,19] in our study, lower LVEF and LAAEV were independently associated with LAAT formation. Similar to previous reports, most patients with LAAT had a CHA_2DS_2-VASc score >2. However, CHA_2DS_2-VASc score was not predictive of LAAT in the present study. Although patients with LAAT more frequently had hypertension, congestive heart failure, vascular disease, and lower LVEF, the mean CHA_2DS_2-VASc score was not significantly different between the 2 groups, consistent with previous observations that individual risk factors in the CHA_2DS_2-VASc score do not carry an equal risk.[21]

The most catastrophic complication of AF is embolic stroke.[22] The detection of LAAT by TEE has important clinical and prognostic implications. Previous studies have established that LAAT is associated with increased risk of thromboembolic events.[13,23] In the present study, we showed that LAAT, LAAEV, and CHA_2DS_2-VASc score were independently associated with increased risk of ischemic stroke. Despite the lack of association with LAAT, CHA_2DS_2-VASc score was a strong predictor of ischemic stroke. This suggests that the association of AF with thromboembolic risk is multifactorial and likely involves risk factors beyond the presence of LAAT and stasis of flow in the LAA.

Patients with AF have a higher mortality rate than those with sinus rhythm.[24] The impact of LAAT on survival has not been specifically assessed previously. Theoretically, stasis of blood flow in the LAA may be a major determinant of excess mortality, potentially attributable to the risk of fatal stroke in patients with AF and greater burden of cardiovascular disease in patient with AF.[25] However, in the present study survival was not significantly different between patients with LAAT versus without LAAT, likely because patients with LAAT are typically monitored more closely and receive more adequate OAC and for a longer period than those without LAAT, which could potentially minimize the risk of death from fatal stroke or subsequent embolization.

The pathogenesis of LAAT formation is a complex and incompletely understood phenomenon. Previous studies have shown that LAA flow velocity is markedly attenuated by elevated left ventricular filling pressure, resulting in LAA stasis, thereby increasing the risk of LAA thrombosis.[26,27] Such a thrombogenic milieu may explain the pathophysiologic mechanism and predisposition for stroke, ostensibly due to thrombus formation in the LAA.[28]

Our findings support broader use of OAC in patients with reduced LVEF and static flow in the LAA, irrespective of CHA_2DS_2-VASc score or duration of AF. As LAAEV is a physiologic measurement of left atrial and diastolic function, we speculate that noninvasive measurements of left atrial and diastolic function (e.g., mitral inflow e-wave, e-wave deceleration time, mitral annular velocity, and left atrial dimension) could potentially serve similar function—that is, as adjunct to established stroke risk assessment tools to guide therapy in AF based on individual risk profiles.

Although our results are based on prospectively collected data, a number of potential limitations should be considered in the interpretation of these findings. Ours was a single-cohort study, which could have site-specific bias. Despite our relatively large sample size, the number of LAAT events was somewhat limited. Our results should therefore be considered hypothesis generating and require confirmation. The TEE procedures were performed during a 12-year period; thus, operator experience and technological advancements may have confounded results. Data regarding the duration or pattern of periprocedural OAC were not available, making it difficult to discern the impact of OAC on LAAT formation. However, the number of patients receiving OAC was similar in both groups, suggesting that other factors, such as AF recurrence and severity of atrial stasis over time, may have had a predominant role. AF duration could not be ascertained accurately from the medical records as many as 50% of cases of AF can be silent,[29] and may explain

the lack of association of AF duration with stroke in our study. Although TEE is the most sensitive and reliable technique to detect LAAT as a potential cardiac source of thromboembolism before ECV, it is a semi-invasive procedure with associated risks.

In conclusion, LAAT in patients who underwent TEE-guided cardioversion is uncommon. The present study showed that reduced LVEF and reduced LAAEV are important pathophysiologic correlates of LAA thrombogenesis and subsequent ischemic stroke in patients who underwent TEE-guided ECV for AF. These findings support broader use of OAC in these patients, irrespective of CHA_2DS_2-VASc score or duration of AF.

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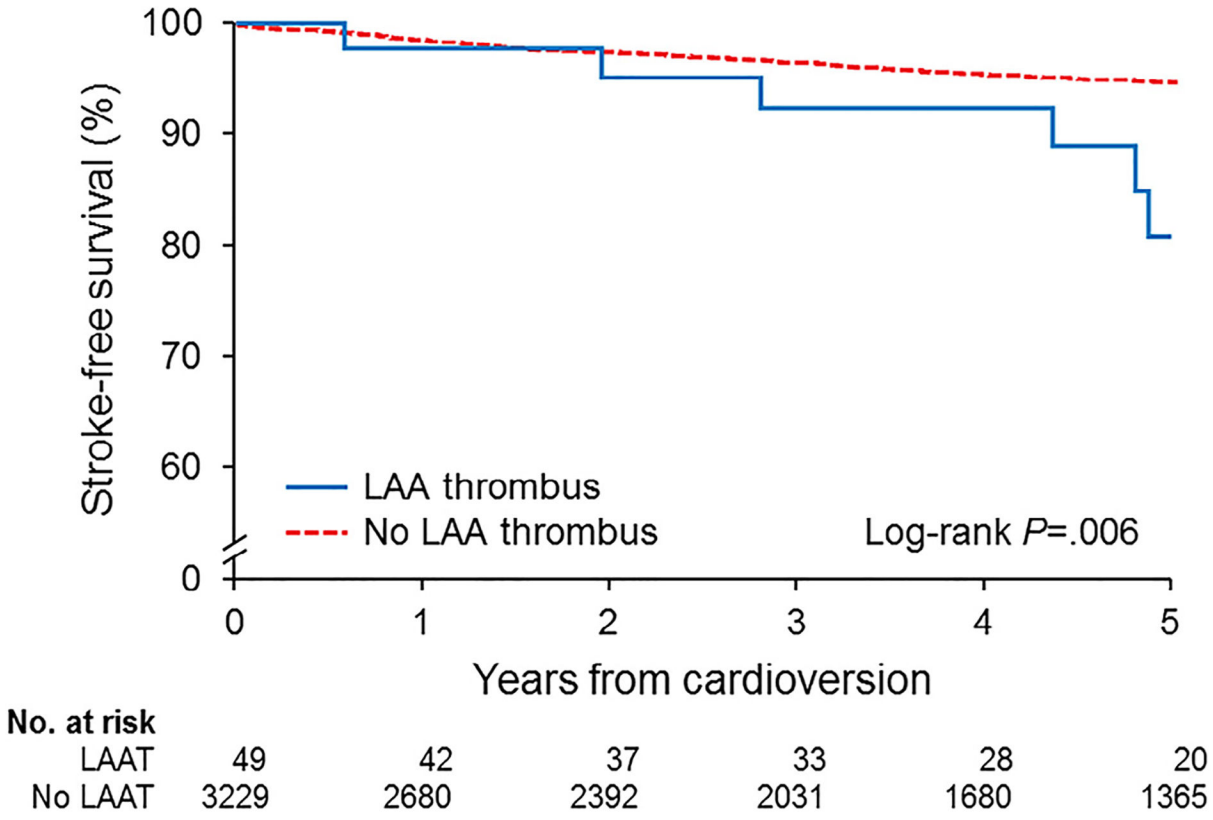

Figure 1.

Kaplan-Meier analysis showing freedom from ischemic stroke in patients with or without LAAT. The survival curves show significantly lower freedom from stroke in the group with LAAT compared with the group without LAAT.

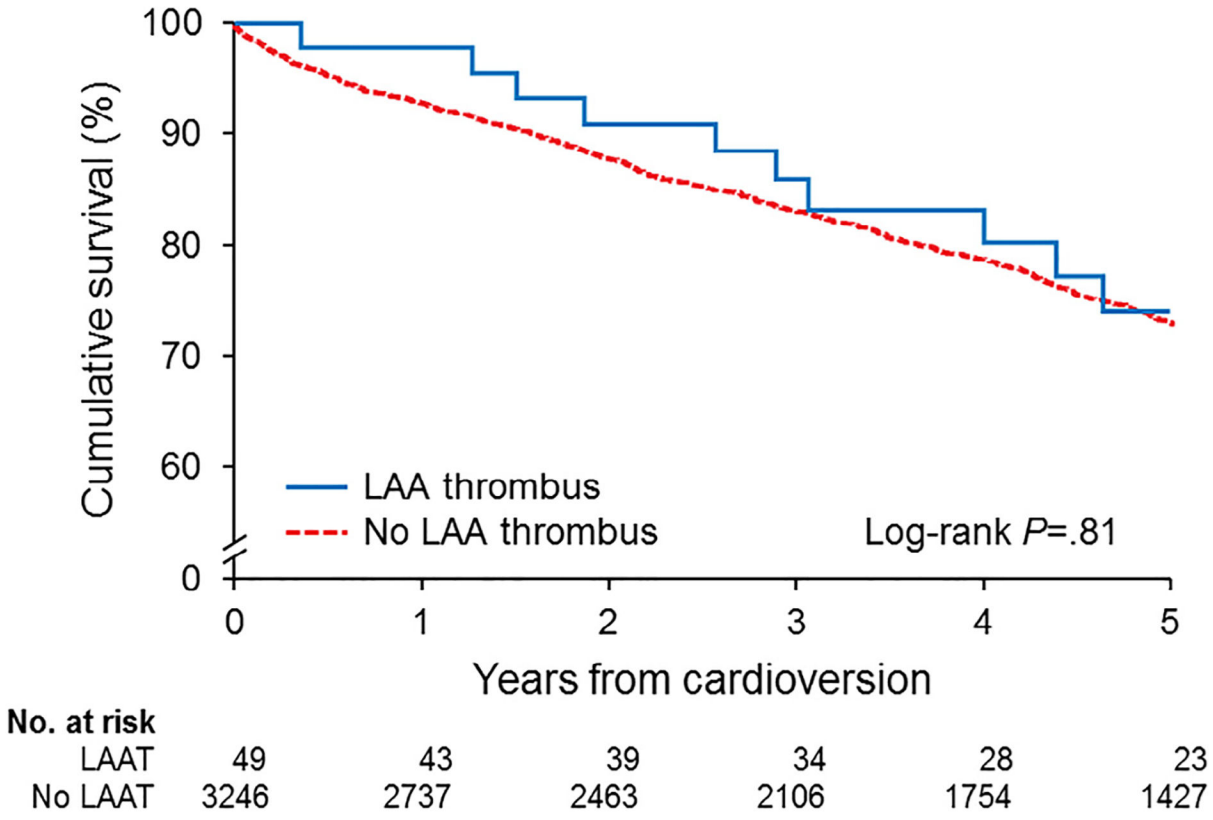

Figure 2.

Kaplan-Meier survival curves of patients with or without LAAT during precardioversion TEE. The survival curves show no significant difference in survival in the group with LAAT versus the group without LAAT.

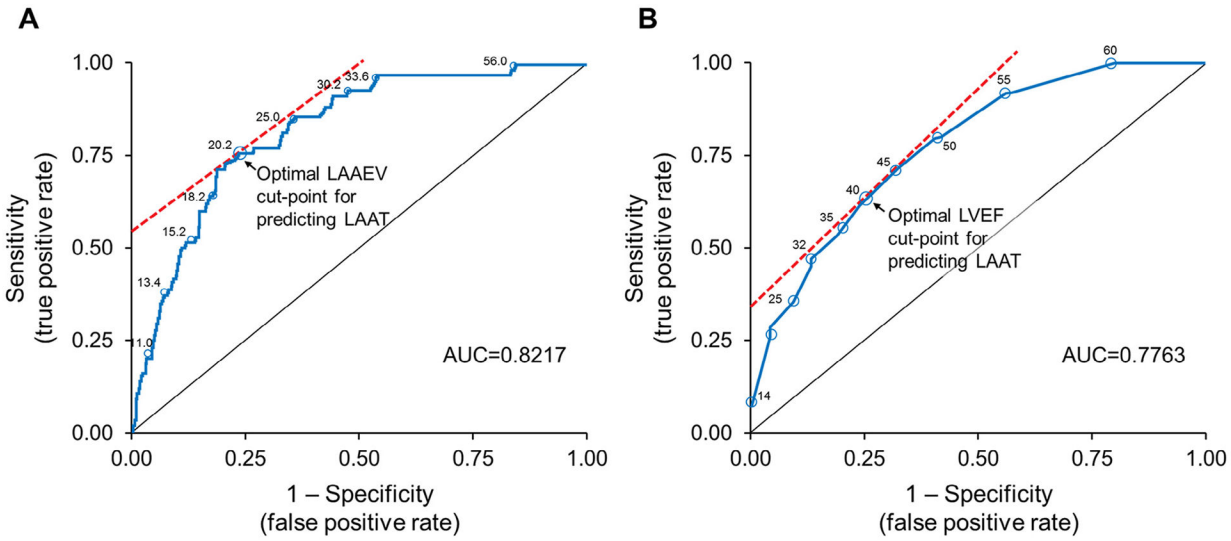

Figure 3.

(A) ROC curve for LAAEV to predict the presence of LAAT in patients with atrial fibrillation who underwent TEE-guided ECV. An LAAEV cut-point of 20.2 cm/s had 75% sensitivity and 77% specificity for predicting LAAT; AUC = 0.822. *(B)* ROC curve for LVEF. An LVEF cut-point of 40% had 62% sensitivity and 75% specificity for predicting LAAT; AUC = 0.776. ROC = receiver operating characteristic.

Table 1

Baseline characteristics

Characteristic	No LAA Thrombus	LAA Thrombus	*P* Value
	(n = 3,275)	(n = 49)	
Age (years)	69.0 ± 12.5	67.8 ± 14.4	.50
Male sex	2,183 (66.7%)	36 (73.5%)	.36
Body mass index (kg/m^2)	30.6 ± 6.8	31.3 ± 8.5	.57
Hypertension	2,187 (66.8%)	41 (83.7%)	.01
Diabetes mellitus	654 (20.0%)	10 (20.4%)	.61
Prior myocardial infarction	528(16.1%)	8 (16.3%)	.59
Cardiomyopathy (ischemic, idiopathic)	767 (23.4%)	25 (51.0%)	<.001
Heart failure	1,408 (43.0%)	35 (71.4%)	<.001
Prior stroke	385 (11.8%)	6 (12.2%)	.82
Smoker (current or former)	1,566 (47.8%)	23 (46.9%)	.51
Chronic lung disease	445 (13.6%)	7 (14.3%)	.83
Obstructive sleep apnea	576 (17.6%)	10 (20.4%)	.57
Peripheral arterial disease	360(11.0%)	7 (14.3%)	.49
Prior coronary bypass	475 (14.5%)	13 (26.5%)	.03
CHA_2DS_2-VASc score	3.2 ± 1.6	3.6 ± 1.4	.06
CHA_2DS_2-VASc score			.26
0	188 (5.7%)	0 (0.0%)	
1	284 (8.7%)	4 (8.2%)	
2	617 (18.8%)	7 (14.3%)	
>2	2,186(66.8%)	38 (77.6%)	
Precardioversion International Normalized Ratio	1.91 ± 0.89	1.80 ± 0.81	.46
Duration of AF episode			.24
>48 hours *	410 (12.5%)	3 (6.1%)	
>2days to <7 days	806 (24.6%)	9 (18.4%)	
>7 days to <1 year	1,470 (44.9%)	28(57.1%)	
>1 year	103 (3.1%)	1 (2.0%)	
Preprocedure medications			

Characteristic	No LAA Thrombus	LAA Thrombus	*P* Value
β-Blocker	1,977 (60.4%)	31 (63.3%)	.66
Calcium-channel blocker (nondihydropyridine)	1,080 (33.0%)	17 (34.7%)	.88
Statin	1,087 (33.2%)	14 (28.6%)	.54
Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker	1,361 (41.6%)	32 (65.3%)	.001
Antiplatelet	1,792 (54.7%)	29 (59.2%)	.57
Warfarin			.29
No Warfarin *	990 (30.2%)	11 (22.4%)	
Warfarin started in hospital	1,279(39.1%)	21 (42.9%)	
Warfarin with subtherapeutic INR	727 (22.2%)	15 (30.6%)	
Warfarin with therapeutic INR	275 (8.4%)	2(4.1%)	
Novel oral anticoagulant	32 (1.0%)	0 (0.0%)	
Antiarrhythmic	1,052(32.1%)	11 (22.5%)	.17
Hemodynamics			
Heart rate (beats/min)	92.7 (22.7)	87.2 (18.5)	.38
Echocardiography	36.6 ± 20.8	17.2 ± 8.5	<.001
Left atrial appendage emptying velocity (cm/s)			
Left atrial appendage emptying velocity			<.001
Tertile 1, ≤20.8 (cm/s)	821 (25%)	39 (79.6%)	
Tertile 2, 20.8–46.4 (cm/s)	1,638 (50.0%)	9 (18.4%)	
Tertile 3, >46.4 (cm/s)	821 (25.1%)	1 (2.0%)	
Spontaneous echo contrast (LA or LAA)	1,423 (43.5%	38 (77.6%)	<.001
Left ventricular ejection fraction (%)	51.4 ± 13.7	39.9 ± 17.6	<.001
Left ventricular ejection fraction ≤40%	745 (22.7%)	24 (49.0%)	<.001
Left atrial enlargement (moderate or higher)	2040 (70.00%)	41 (93.2%)	<.001
Mitral regurgitation (moderate or higher)	844 (25.8%)	19 (38.8%)	.05
INR at discharge	1.95 ± 0.85	1.94 ± 0.71	.52
Discharge medications			
β-Blocker	1,937(59.1%)	33 (67.3%)	.24
Calcium-channel blocker (nondihydropyridine)	608 (18.6%)	11 (22.4%)	.47
Statin	1,183 (36.1%)	13 (26.5%)	.18
Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker	1,554 (47.5%)	30 (61.2%)	.06

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Characteristic	No LAA Thrombus	LAA Thrombus	P Value
Antiplatelet	1,707 (52.1%)	30(61.2%)	.25
Low-molecular-weight heparin	1,076 (32.9%)	24 (49.0%)	.03
Warfarin	2,861 (87.4%)	47 (95.9%)	.12
Novel oral anticoagulant	39 (1.2%)	0 (0.0%)	
Antiarrhythmic	1,143 (34.9%)	12 (24.5%)	.17

Values are mean (SD), median (IQR) or n (%).

Hypertension was defined in accordance with 2016 ACC/AHA guidelines.

* Reference category.

Table 2

Univariate analysis for the prediction of LAA thrombus, ischemic stroke, and death

Characteristic	LAA Thrombus (n = 49) Odds ratio (95% CI)	*P* Value	Ischemic Stroke (n = 182) Hazard ratio (95% CI)	*P* Value	Death (n = 1,118) Hazard ratio (95% CI)	*P* Value
Demographics						
Age	1.00 (0.98–1.02)	.80	1.04 (1.02–1.05)	<.001	1.07 (1.06–1.07)	<.001
Male sex	1.32 (0.78–2.24)	.30	0.79 (0.59–1.07)	.13	0.83 (0.73–0.93)	.002
Body mass index	1.00 (0.95–1.04)	.86	1.00 (0.98–1.02)	.99	0.97 (0.96–0.98)	<.001
Hypertension	2.19(1.17–4.09)	.01	1.46 (1.05–2.03)	.02	1.32(1.16–1.50)	<.001
Diabetes mellitus	0.87 (0.48–1.60)	.66	0.98 (0.67–1.43)	.90	1.58 (1.38–1.80)	<.001
Prior myocardial infarction	1.56 (0.89–2.75)	.12	1.47(1.02–2.11)	.04	1.79 (1.56–2.06)	<.001
Cardiomyopathy (ischemic, idiopathic)	3.41 (1.93–6.00)	<.001	0.77(0.53–1.11)	.17	1.15 (1.01–1.32)	.04
Heart failure	3.43 (2.00–5.87)	<.001	1.22 (0.91–1.63)	.19	1.61 (1.43–1.81)	<.001
Prior stroke	1.05 (0.52–2.13)	.88	2.10(1.46–3.02)	<.001		
Smoker	1.08 (0.74–1.56)	.70	1.12(0.84–1.50)	.43	1.15 (1.02–1.29)	.02
Chronic lung disease	1.28 (0.70–2.35)	.42	1.14(0.72–1.80)	.58	1.80(1.54–2.11)	<.001
Obstructive sleep apnea	0.89 (0.50–1.61)	.71	1.28 (0.88–1.85)	.20	0.88 (0.74–1.04)	.13
Peripheral arterial disease	1.35 (0.60–3.03)	.47	1.39(0.91–2.14)	.13	1.77(1.51–2.08)	<.001
Prior coronary bypass	2.71 (1.62–4.52)	<.001	1.34 (0.93–1.99)	.12	2.01 (1.75–2.31)	<.001
CHA_2DS_2-VASc score	1.17(1.01–1.36)	.04	1.24(1.13–1.36)	<.001	1.38 (1.33–1.43)	<.001
0 *						
1 *			2.13 (0.59–7.74)	.25	2.03 (1.16–3.56)	.01
2	0.81 (0.23–2.77)	.73	3.17(0.97–0.37)	.06	2.57(1.53–4.31)	<.001
>2	1.23 (0.44–3.48)	.69	4.46 (1.42–14.01)	.01	5.44 (3.32–8.92)	<.001
Duration of atrial fibrillation episode						
>48 h (vs <48 h)	1.62 (0.88–2.96)	.12			0.96 (0.83–1.09)	.51
<48 h *						
>2 days to <7 days			0.90 (0.56–1.44)	.66	1.08 (0.89–1.32)	.43
>7 days to <1 year			0.80 (0.52–1.23)	.30	0.91 (0.75–1.09)	.31
>1 year			0.46(0.14–1.50)	.20	0.81 (0.54–1.22)	.31

Characteristic	LAA Thrombus (n = 49) Odds ratio (95% CI)	*P* Value	Ischemic Stroke (n = 182) Hazard ratio (95% CI)	*P* Value	Death (n = 1,118) Hazard ratio (95% CI)	*P* Value
Preprocedure medications						
β-Blocker	1.52 (0.91–2.54)	.11	1.40 (1.03–1.90)	.03	0.92 (0.82–1.04)	.17
Calcium-channel blocker (nondihydropyridine)	1.16(0.71–1.89)	.56	1.48(1.10–1.99)	.01	0.99(0.87–1.12)	.89
Statin	0.85 (0.51–1.41)	.53	0.95 (0.69–1.32)	.76	0.93 (0.81–1.06)	.28
Angiotensin converting enzyme inhibitor or Angiotensin II receptor blocker	2.53 (1.54–4.15)	<.001	1.12(0.83–1.50)	.46	1.21 (1.07–1.36)	.002
Antiplatelet	1.60 (0.97–2.62)	.06	1.01 (0.75–1.35)	.95	1.22 (1.09–1.38)	.001
Warfarin	1.11 (0.48–2.57)	.81			0.92 (0.86–0.98)	.006
Antiarrhythmic	0.66(0.39–1.12)	.12	0.75 (0.54–1.05)	.09	0.94 (0.83–1.07)	.37
Hemodynamics						
Heart rate^{-1}	1.01 (0.99–1.03)	.32	1.00 (0.99–1.01)	.90	0.997 (0.994–0.999)	.01
Echocardiography						
Left atrial appendage emptying velocity^{-1}	1.12(1.09–1.15)	<.001	1.01 (1.01–1.02)	.003	1.01 (1.01–1.02)	<.001
Tertile 1, ≤20.8	78.21 (10.72–570.33)	<.001	1.56(1.11–2.19)	.009		
Tertile 2, 20.8–46.4	13.55 (1.72–107.15)	.01	1.42 (0.97–2.07)	.07		
Tertile 3, >46.4 *						
Spontaneous echo contrast (LA or LAA)	5.17 (2.70–9.88)	<.001	1.40 (1.01–1.95)	.004	1.24 (1.08–1.42)	.002
Left atrial thrombus	3.28 (1.77–6.07)	<.001	6.89 (0.96–49.19)	.05	2.50 (0.63–10.02)	.20
Left atrial appendage thrombus			2.74 (1.29–5.83)	.009	1.06 (0.66–1.71)	.80
Ejection fraction^{-1}	1.05 (1.03–1.06)	<.001	1.00 (0.99–1.01)	.67	1.01 (1.01–1.02)	.002
Ejection fraction ≤40%	3.37 (1.89–6.01)	<.001	0.85 (0.59–1.22)	.37	1.26(1.10–1.44)	.001
Mitral regurgitation (≥moderate)	1.27 (0.76–2.12)	.37	1.15 (0.84–1.58)	.38	1.42 (1.26–1.60)	<.001
International Normalized Ratio at discharge	1.08 (0.81–1.45)	.60	1.03 (0.85–1.23)	.80	1.09(1.01–1.17)	.03

CI = confidence interval.

*Reference category.

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Table 3

(A) Multivariate regression analysis for the prediction of left atrial appendage thrombus (stepwise logistic), ischemic stroke, and death (Cox) (model 1).
(B) Multivariate regression analysis for the prediction of left atrial appendage thrombus (stepwise logistic), ischemic stroke, and death (Cox) (model 2)

A						
Variables	Left atrial appendage thrombus		Ischemic Stroke		Death	
	(n = 49)	*P* Value	(n = 182)	*P* Value	(n = 1,118)	*P* Value
	Odds ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
CHA_2DS_2-VASc score						
0 *						
1 *,†			2.30 (0.63–8.35)	.21	2.03 (1.16–3.57)	.01
2	0.56(0.18–1.63)	.50	3.19 (0.97–10.49)	.06	2.32 (1.38–3.92)	.002
>2	0.65 (0.19–2.30)	.29	4.35 (1.38–13.76)	.01	4.96(3.02–8.15)	<.001
Left atrial appendage emptying velocity						
Tertile 3, >34 *						
Tertile 2, 20.3–33.9	12.19(1.53–96.86)	.02	1.21 (0.81–1.81)	.36	1.21 (1.04–1.39)	.02
Tertile 1, ≤20.2	65.85 (8.93–485.39)	<.001	1.46 (1.03–2.07)	.03	1.39(1.19–1.62)	<.001
Ejection fraction ≤40%	2.48 (1.38–4.46)	<.001	0.72 (0.50–1.05)	.09	1.09 (0.95–1.25)	.23
Left atrial appendage thrombus			2.84 (1.30–6.19)	.009	0.86(0.51–1.39)	.51
C-statistic	0.849		0.726		0.859	
B						
Variables	Left atrial appendage thrombus		Ischemic Stroke		Death	
	(n = 49)	*P* Value	(n = 182)	*P* Value	(n = 1,118)	*P* Value
	Odds ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
Congestive heart failure or Ejection fraction ≤40%	1.78 (1.28–3.53)	.03	1.10(0.82–1.47)	.55	1.52(1.36–1.69)	<.001
Hypertension	1.65 (1.07–5.41)	.04	1.32 (0.93–1.87)	.12	.98(0.87–1.12)	.79
Age > = 75 years			2.06 (1.40–3.03)	<.001	3.76 (3.20–4.43)	<.001
Diabetes			1.19(0.83–1.69)	.35	1.39 (1.22–1.58)	<.001
Prior Stroke			1.83 (1.28–2.62)	.001	1.24 (1.07–1.43)	.005
Vascular disease			1.15 (0.85–1.56)	.36	1.52(1.35–1.71)	<.001
Age 65–74 y			1.21 (0.80–1.82)	.37	1.83 (1.55–2.18)	<.001
Sex (female)			1.17(0.86–1.59)	.33	1.04(0.92–1.17)	.57

Left atrial appendage emptying velocity						
Tertile 3, >34 *						
Tertile 2, 20.3–33.9			1.24 (0.88–1.73)	.22	1.10(0.96–1.24)	.18
Tertile 1, ≤20.2	56.81 (7.66–421.57)	<.001	1.32 (1.02–1.87)	.03	1.19(1.03–1.36)	.02
Left atrial appendage thrombus			3.21 (1.48–6.95)	.003	1.10(0.67–1.78)	.71
C-statistic	0.844		0.704		0.842	

CI = confidence interval.

*Reference category.

†CHA_2DS_2-VASc score reference value for LAA thrombus (0–1).