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Abbreviated title: LASEC as a predictor of 5-year stroke/death in NVAF

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Summary

Background. – Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) can be used to detect the presence of left atrial thrombus and left atrial spontaneous echocardiographic contrast (LASEC).

Aim. – To evaluate the prognostic value of TTE and TOE in predicting stroke and all-cause death at 5-year follow-up in patients with non-valvular atrial fibrillation (NVAF).

Methods. – This study included patients hospitalized with electrocardiography-diagnosed NVAF in Saint-Antoine University Hospital, Paris, between July 1998 and December 2011, who underwent TTE and TOE evaluation within 24 hours of admission. Cox proportional-hazards models were used to identify predictors of the composite outcome (stroke or all-cause death).

Results. – During 5 years of follow-up, stroke/death occurred in 185/903 patients (20.5%). By multivariable analysis, independent predictors of stroke/death were CHA_2DS_2-VASc score (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.25–1.47; $P < 0.001$), left atrial area > 20 cm^2 (HR 1.59, 95% CI 1.08–2.35; $P = 0.018$), moderate LASEC (HR 1.72, 95% CI 1.13–2.62; $P = 0.012$) and severe LASEC (HR 2.04, 95% CI 1.16–3.58; $P = 0.013$). Independent protective predictors were dyslipidaemia (HR 0.60, 95% CI 0.43–0.83; $P = 0.002$) and discharge prescription of antiarrhythmics (HR 0.59, 95% CI 0.40–0.87; $P = 0.008$). Adding LASEC to the CHA_2DS_2-VASc score modestly improved predictive accuracy and risk classification, with a C index of 0.71 vs 0.69 ($P = 0.004$).

Conclusions. – In this retrospective monocentric study, the presence of moderate/severe LASEC was an independent predictor of stroke/death at 5-year follow-up in patients with NVAF. The inclusion of LASEC in stroke risk scores could modestly improve risk stratification.

Résumé

Contexte. – L'échocardiographie transthoracique (ETT) et transoesophagienne (ETO) peuvent être utilisées pour détecter la présence d'un thrombus et le contraste spontané dans l'oreillette gauche (CS OG).

Objectif. – Le but de l'étude est d'évaluer la valeur pronostique de l'ETT et de l'ETO, pour prédire la survenue d'un AVC et la mortalité toute cause à 5 ans de suivi, chez le patient en FA non valvulaire (FANV).

Méthodes. – L'étude a inclus des patients hospitalisés pour FA non valvulaire (diagnostiqué par électrocardiogramme) au sein de l'Hôpital Universitaire Saint Antoine, Paris, entre juillet 1998 et décembre 2011 et qui ont eu une ETT-ETO dans les 24 heures après l'admission. Un modèle de régression de Cox a été utilisé pour identifier les prédicteurs du critère composite : infarctus cérébral ou mortalité toute cause.

Résultats. – Durant les 5 années de suivi, l'infarctus cérébral/décès est survenu pour 185/903 patients (20,5 %). En analyse multivariée, les facteurs prédicteurs indépendants d'infarctus cérébral/décès étaient le score CHA_2DS_2-VASc (hazard ratio [HR] 1,35, intervalle de confiance à 95 % [IC 95 %] 1,25–1,47; $P < 0,001$), une oreillette gauche > 20 cm² (HR 1,59, IC 95 % IC 1,08–2,35 ; $P = 0,018$), un CS OG moyen (HR 1,72, IC 95 % 1,13–2,62 ; $P = 0,012$) et CS OG sévère (HR 2,04, IC 95 % 1,16–3,58 ; $P = 0,013$). Les facteurs indépendants protecteurs étaient la dyslipidémie (HR 0,60, IC 95 % 0,43–0,83 ; $P = 0,002$) et la prescription d'antiarythmiques à la sortie d'hospitalisation (HR 0,59, IC 95 % 0,40–0,87 ; $P = 0,008$). L'ajout du CS OG au score CHA_2DS_2-VASc améliore modestement la précision et la classification du risque, avec un C index à 0,71 vs 0,69 ($P = 0,004$).

Conclusions – La présence d'un CS OG moyen/sévère est un prédicteur fort et indépendant d'infarctus cérébral/décès à 5 ans de suivi chez le patient en FA non valvulaire. L'inclusion du CS OG dans les scores de risque thromboembolique pourrait améliorer la stratification du risque.

KEYWORDS

Atrial fibrillation;

Thromboembolic risk;

Echocardiography;

CHA_2DS_2-VASc score;

Reassessment

MOTS CLÉS

Fibrillation atriale ;

Risque thrombo-embolique ;

Échocardiographie ;

CHA_2DS_2-VASc score ;

Reclassification

Abbreviations: AF, atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke (Doubled); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 years and Sex category (Female); CI, confidence interval; HR, hazard ratio; LAA, left atrial appendage; LASEC, left atrial spontaneous echocardiographic contrast; LAT, left atrial thrombus; LVEF, left ventricular ejection fraction; NVAF: non-valvular atrial fibrillation; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Background

Atrial fibrillation (AF) is a common arrhythmia, affecting 1–2% of the general population [1, 2], and is responsible for significant morbidity and mortality and reduced quality of life [3, 4]. The risk of ischaemic stroke in patients with non-valvular atrial fibrillation (NVAF) is increased in those with risk factors such as previous stroke, advanced age and the presence of co-morbidities, but can be reduced by the administration of anticoagulant therapy [5, 6]. Clinical scores currently used to determine individualized thromboembolic risk include the $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke [Doubled]) [5] and, more recently, the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 years and Sex category [Female]) [7].

Echocardiographic prognostic factors for thromboembolic risk were identified using the results from the Stroke Prevention in Atrial Fibrillation (SPAF)-II study [8], and included moderate-to-severe left ventricular systolic dysfunction as an independent risk factor for stroke. Bernhardt et al. [9] reported that the presence of a thrombus or left atrial spontaneous echocardiographic contrast (LASEC) on transoesophageal echocardiography (TOE) was associated with a high risk of stroke in patients with NVAF. Other echocardiographic risk factors are the presence of significant aortic atheroma or reduced left atrial appendage (LAA) emptying velocity [10]. In clinical practice and in usual risk scores, besides left ventricular ejection fraction (LVEF) < 40%, ultrasound data are poorly used in the stratification of thromboembolic risk and in the decision to initiate anticoagulant therapy.

The aim of this prospective single-centre observational study was to determine whether echocardiographic thromboembolic risk factors, such as LASEC, can improve the prediction of stroke and all-cause death at 5-year follow-up in patients with NVAF.

Methods

Study population

The Atrial Fibrillation and FLUtter And ThromboEmbolism (AFFLUATE) study is a longitudinal prospective observational cohort study designed to evaluate predictors of stroke in patients with atrial arrhythmia [11]. Between July 1998 and December 2011, patients with non-precipitated NVAF (diagnosed on a qualifying electrocardiogram) were hospitalized in the Cardiology Department of Saint-Antoine University Hospital in Paris, France. We defined a precipitated AF event as AF occurring

immediately after surgery, acute myocardial infarction, acute infection, acute alcohol consumption, thyrotoxicosis, acute pericardial disease, acute pulmonary embolism and other acute pulmonary pathology.

Patients' medical history and baseline characteristics were systematically recorded in a database. Clinical risk factors were determined, and the patients' CHA_2DS_2-VASc scores were calculated. All patients were evaluated with transthoracic echocardiography (TTE) within 24 hours of admission and TOE during hospitalization.

The type of AF was determined according to the guidelines [12] as paroxysmal, persistent or permanent AF. The ethics committee of Saint-Antoine University Hospital approved the study. All patients provided informed consent to participate.

TTE

Two-dimensional TTE was performed with commercially available echocardiographic systems (ACUSON Sequoia, Siemens Medical Solutions, Mountain View, CA, USA; and VIVID 7/VingMed System V, General Electric, Horten, Norway) using a 2 Mhz or 2.5 Mhz phased array transducer. Echocardiographic images were obtained in standard parasternal and apical views, and were stored digitally. Echocardiographic measurements were collected according to the American Society of Echocardiography guidelines [13, 14]. LVEF (by Simpson's biplane in the apical view) and left atrial dimension (area in the four-chamber view) were determined.[13, 14]

TOE

TOE examination was performed with the patient under light conscious sedation, and with topical anaesthesia of the hypopharynx with lidocaine spray. TOE was performed according to standard practice [15]. The presence of aortic atheroma or aortic plaque, left atrial thrombus (LAT) and LASEC was recorded. The ascending aorta, aortic arch and descending thoracic aorta were imaged in short- and long-axis views. Atherosclerosis of aortic plaque was defined as irregular intimal thickening with increased echogenicity [15]. Complex atherosclerosis or complex aortic plaque was defined as the presence of protruding atheroma ≥ 4 mm in thickness or as the presence of a mobile aortic thrombus [16]. LAT was defined as a circumscribed and uniformly echo-dense intracavitary mass distinct from the underlying left atrial or LAA endocardium and the pectinate muscles. LASEC was considered

present when dynamic “smoke-like” echoes were seen. The severity of LASEC was graded from 0 to 3 by two observers, according to the Fatkin classification [17]: 0 = none (no echogenicity); 1 = mild LASEC (minimal echogenicity located in the LAA or sparsely distributed in the main cavity of the left atrium; may be detectable only transiently during the cardiac cycle; imperceptible at operating gain settings for two-dimensional echocardiographic analysis); 2 = moderate LASEC (dense swirling pattern in the LAA; generally associated with somewhat lesser intensity in the main cavity; may fluctuate in intensity but detectable constantly throughout the cardiac cycle); 3 = severe LASEC (intense echodensity and very slow swirling patterns in LAA, usually with similar density in the main cavity).

Follow-up and outcomes

All patients were followed for ≥ 6 months or until death. Follow-up data were collected from the patients’ hospital records, from the referring physicians or through structured telephone calls with the patient. Data pertaining to each patient’s clinical status, the occurrence of adverse events and drug therapies were collected. The composite outcome was the first clinical event (stroke or all-cause death) occurring within the first 5 years of follow-up. The individual components of the composite outcome were also assessed.

Statistical analysis

In this study, only patients who underwent TTE and TOE were included in the analysis. Patient characteristics, stratified by occurrence of the composite outcome, are reported as counts and percentages for categorical variables and as means ± standard deviations or medians (interquartile ranges) for continuous variables. Survival curves were obtained from Kaplan-Meier estimates, and were compared using the log-rank test. Factors associated with presence of LASEC were assessed using logistic regression models. Associations between baseline variables and outcomes were evaluated using univariate Cox proportional-hazards models. A multivariable Cox model, including the CHA_2DS_2-VASc score and variables not included in the CHA_2DS_2-VASc score with $P < 0.10$ in the univariate analyses (AF type, dyslipidaemia, left atrial area, LASEC and vitamin K antagonists, antiplatelet drugs or antiarrhythmic drugs at discharge), was used to identify independent predictors of the composite outcome. A new risk-stratification scheme was created by adding one point to the

CHA_2DS_2-VASc risk score when LASEC was mild or moderate and two points when LASEC was severe, according to their respective hazard ratios (HRs) in the multivariable Cox model. To compare the predictive ability of the risk-stratification schemes, the predictive accuracy of the models' C indexes were calculated and compared.

All statistical analyses were performed using STATA V12 statistical software (StataCorp LP, College Station, TX, USA).

Results

Study population

Between July 1998 and December 2011, 1212 patients with non-precipitated NVAF were hospitalized, of whom 903 patients (74.5%) underwent TTE and TOE. The mean age of the study population was 66.1 ± 14.3 years, and 520 (57.6%) were men. At baseline, 331 patients (36.7%) had paroxysmal AF, 392 (43.4%) had persistent AF and 180 (19.9%) had permanent AF. Cardioversion to sinus rhythm was spontaneous in 331 patients (36.7%), and was achieved through pharmacological means in 167 (18.5%) or by direct current cardioversion in 224 (24.8%). There was no attempt to perform cardioversion in 96 patients (10.6%), and 85 (9.4%) had a failed pharmacological and/or external electric shock cardioversion.

Baseline clinical and echocardiographic characteristics

Clinical and echocardiographic characteristics according to the absence or presence of the composite outcome at 5-year follow-up are provided in Table 1. The clinical characteristics differed widely between the two groups; for example, patients who had an event during follow-up were significantly older and more likely to have hypertension, diabetes, congestive heart failure and permanent AF. The echocardiographic variables were also different between the two groups. TTE variables associated with a higher risk of the composite outcome were left atrial area > 20 cm^2 and LVEF < 40%. TOE variables associated with a higher risk of the composite outcome were LASEC and complex aortic atheroma (plaque ≥ 4 mm or mobile aortic thrombus). LAT, which was detected in 16 patients (1.8%), was not associated with the composite outcome.

Clinical outcomes

The median follow-up was 5.8 (3.4–9.0) years. During the first 5 years of follow-up, the composite outcome (stroke or death) occurred in 185 patients (20.5%), and was more frequent in patients with LASEC (28.5% vs 13.0%); the rate increased with increasing LASEC severity (Table A.1). One hundred and sixty-two patients (17.9%) died and 25 (2.8%) had a stroke; the rates of all-cause death and stroke increased with increasing LASEC severity (Table A.1). The Kaplan-Meier survival curves up to 5 years for the composite endpoint are shown in Fig. 1. Rates of the composite outcome and its components per 100 patient-years increased with increasing LASEC grade (Fig. 2).

Predictors of stroke or all-cause death

On univariate analysis, higher CHA_2DS_2-VASc score, permanent AF and antiplatelet drugs at discharge were associated with a higher risk of the composite outcome, whereas the presence of dyslipidaemia and vitamin K antagonist or antiarrhythmic drug at discharge were protective. In a supplementary analysis, where components of the CHA_2DS_2-VASc score were included separately, all CHA_2DS_2-VASc components apart from sex were significantly predictive of the composite outcome on univariate analysis (Table 2 and Table A.2). TTE variables associated with a higher risk of the composite outcome on univariate analysis were LVEF < 40% (HR 2.42, 95% CI 1.69–3.48; P < 0.0001) and left atrial area > 20 cm^2 (HR 2.42, 95% CI 1.74–3.35; P < 0.0001). LASEC severity (increasing HRs with increasing severity) and aortic atheroma ≥ 4 mm (HR 2.31, 95% CI 1.62–3.27; P < 0.0001) were associated with an increased risk of the composite outcome, with severe LASEC being the strongest prognostic factor in TOE (Table 2 and Table A.2). In the multivariable logistic regression analysis, CHA_2DS_2-VASc score (per unit increase), left atrial area > 20 cm^2 and moderate or severe LASEC remained significant predictors of increased risk of the composite outcome, whereas dyslipidaemia and antiarrhythmic drug at discharge remained protective (Table 2).

If we merge moderate and severe LASEC, the HR should be 2.98 (95% CI 2.11–4.23; P < 0.0001) in univariate analysis and 1.79 (95% CI 1.20–2.67; P = 0.0004) in multivariable analysis.

Subgroup of patients with CHA_2DS_2-VASc score ≤ 1

Among the 280 patients with CHA_2DS_2-VASc score ≤ 1, we found no significant difference in the composite outcome by LASEC presence/severity, and LASEC was not predictive of increased risk of the composite outcome by multivariable logistic regression analysis (Table A.3 and Table A.4).

Additional prognostic value of adding LASEC to the CHA_2DS_2-$VASC_2$ risk score

Adding LASEC presence and severity to the CHA_2DS_2-VASc score modestly, but significantly, improved the predictive accuracy and risk classification, with a C index of 0.71 vs 0.69 ($P = 0.004$). The comparison of the CHA_2DS_2-VASc score and the score adding LASEC with the annual stroke rate in the population is presented in Table A.5.

Discussion

The results of this single-centre prospective observational study show that the presence of LASEC on TOE is an independent predictor of stroke and all-cause death in patients with NVAF at long-term follow-up. This variable could be used, in addition to the CHA_2DS_2-VASc score, to further stratify patients with NVAF according to their individual thromboembolic risk.

Left atrial size, presence of LAT and cardiovascular risk

In this study of 903 patients, we found a correlation between the presence of LASEC and the composite outcome; this was driven primarily by death, as only 25 patients (2.8%) had a stroke during the first 5 years of follow-up.

One of 205 patients (0.5%) classified as at low stroke risk according to $CHADS_2$ (score = 0) had a LAT; and two of the 150 patients (1.3%) with a CHA_2DS_2-VASc score of 1 had a LAT. Rader et al. [18] reported a 3% prevalence of LAT among patients with a $CHADS_2$ score of 0, and Providencia et al. [19] a prevalence of 4.2% among those with a $CHADS_2$ score of 0 and of 5.0% among those with a CHA_2DS_2-VASc score of 1. The presence of a LAT increases the risk of stroke 2.5- to 3-fold [20], necessitating the use of effective anticoagulation. However, the risk of LAT in patients classified as at low risk on clinical risk scores is often underestimated. These findings suggest that simple stratification using thromboembolic risk scores is insufficient, especially in patients classified as at low clinical risk. In our study, we found that the increased risk of stroke among patients with LAT was not statistically significant, probably because of a power issue.

A supplementary analysis that included the individual variables from the CHA_2DS_2-VASc score – instead of the score itself – showed increased cardiovascular risk for patients with LVEF < 40% (Table A.2). Indeed, left ventricular systolic dysfunction is a prognostic factor for mortality [7] and stroke [21]

in patients with NVAF. In addition, left atrial area > 20 cm^2 was also predictive of increased cardiovascular risk in the multivariable analysis (Table 2). In other studies, analysis of left atrial volume has shown that left atrial dilatation ≥ 32 mL/m^2 is an independent risk factor for stroke [22, 23]. Thus, left ventricular systolic dysfunction associated with dilatation of the left atrium is involved in blood stasis, favouring thrombus formation.

LASEC as a predictor of cardiovascular events

In the univariate analysis, the presence of LASEC increased the cardiovascular risk, with the HRs rising with increasing severity of LASEC. By multivariable analysis, severe LASEC doubled the risk of stroke/death in the overall population, but not in the subgroup of patients with a CHA_2DS_2-VASc score ≤ 1. Few studies have established the prognostic role of LASEC in predicting stroke or death in patients with AF. Dawn et al. [24], in a study involving 175 patients with AF and mild mitral regurgitation (grade < 2), showed that LASEC and LAT were predictors of cardiovascular mortality: relative risk 7.96, 95% CI 1.55–40.7 (P = 0.013); and relative risk 5.52, 95% CI 1.26–24.3 (P = 0.024), respectively. Khumri et al. [25], in a study involving 524 patients with NVAF, reported a prognostic role of LASEC for all-cause death (relative risk 1.57, 95% CI 1.00–2.51; P = 0.057).

In our study, all 16 patients with LAT also had LASEC. This finding is not surprising as the link between LAT and LASEC has been reported [26]. A recent study [27] showed that the presence and degree of LASEC were associated with an initially more severe stroke and worse functional outcome at 3 months after stroke onset. However, 46.5% of the patients with NVAF did not undergo TOE in this series.

To date, no guidelines have been put forward to guide the treatment, including cardioversion, of patients with AF and LASEC. Patel and Flaker [28] published a review of nine studies, in which they found no higher risk of cardiovascular events after cardioversion in patients with LASEC without thrombus; however, only one of the nine studies was randomized, and the different grades of LASEC were not taken into account. In contrast, based on TOE variables, good results of cardioversion have been reported after the exclusion of patients with LASEC or low-flow LAA velocities.[29, 30]

Study limitations

This study has several limitations. First, it was a single-centre study, and the results may, therefore, not be generalizable to all patients with NVAF. Second, anticoagulation status at follow-up was missing in 7.4% of patients without events during follow-up and in 9.0% of patients with an event; and for patients under anticoagulation therapy, we could not assess the time in the therapeutic range. Also, we cannot exclude the possibility that the increased rate of events in patients presenting with LASEC at baseline resulted from a lack or misuse of anticoagulation treatment. Third, during the inclusion period of our study (1998–2011), first-line imaging was both TTE and TOE. Nowadays, computed tomography and cardiac magnetic resonance imaging of heart cavities are widely used. We did not have computed tomography or cardiac magnetic resonance evaluation because this evaluation was not very common at the time of our study. Fourth, the stroke rate in our population with a median CHA_2DS_2-VASc of 2 is relatively low (2.8% over 5 years). We could explain this incidence of stroke by the improvement in AF management (therapeutic with anticoagulation versus aspirin, score risk using CHA_2DS_2-VASc versus $CHADS_2$) and management of cardiovascular risk factors during the years of the study. Fifth, the primary endpoint used in our study was a combined criterion (stroke/death). Also refined risk classification, with addition of LASEC to an isolated risk score of stroke and not death (CHA_2DS_2-VASc), could be discussed. Nevertheless the improvement in stroke risk stratification with the addition of LASEC (C index of 0.71 vs 0.69; $P = 0.004$) is interesting, and needs further investigation. Sixth, no significant association was found between LAT and risk of stroke or death. This is most likely because of a lack of power, as few thrombi were detected at baseline. Also, we did not assess the prognostic consequences of “sludge” in the LAA, reported to be independently associated with thromboembolic complications and all-cause mortality [31]. Nor did we assess the effect of other potentially useful TOE variables (e.g. LAA velocities). Lastly, it is not known how many deaths had cardiovascular causes and, therefore, were potentially related to LASEC.

Conclusions

The results of this prospective study confirm the prognostic value of the CHA_2DS_2-VASc score in patients with NVAF for the composite endpoint of stroke or all-cause death. The findings also show that the presence and severity of LASEC may also be prognostic of stroke or death. The inclusion of echocardiographic markers in existing risk scores, to further refine risk stratification in patients with AF, should therefore be further investigated.

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Disclosure of interest

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The other authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Kaplan-Meier survival curves for the composite endpoint (stroke or all-cause death) according to left atrial spontaneous echocardiographic contrast (LASEC) grade.

Figure 2. Rates of the composite endpoint and its components (stroke or all-cause death) per 100 person-years. CI: confidence interval; LASEC: left atrial spontaneous echocardiographic contrast.

Table 1 Clinical baseline and echocardiographic characteristics according to the absence or presence of the composite outcome (stroke or death) at 5-year follow-up.

	No event (n = 718)	Event (n = 185)	P[a]
Men[b]	423 (58.9)	97 (52.4)	0.19
Age (years)[b]	63.9 ± 14.3	74.8 ± 10.2	< 0.0001
Hypertension[b]	366 (51.0)	125 (67.6)	< 0.0001
Diabetes mellitus[b]	110 (15.3)	42 (22.7)	0.01
Dyslipidaemia[c]	266 (37.1)	53 (28.7)	0.023
Current smoker	115 (16.0)	25 (13.5)	0.52
Concomitant disease[d]			
AF alone	537 (74.8)	89 (48.1)	< 0.0001
AF and congestive heart failure[b]	100 (13.9)	66 (35.7)	< 0.0001
Previous disease[e]			
Stroke or TIA[b]	41 (5.7)	20 (10.8)	0.015
Acute coronary syndrome[b]	63 (8.8)	35 (18.9)	< 0.0001
Congestive heart failure[b]	18 (2.5)	19 (10.3)	< 0.0001
Type of AF			0.0003
Paroxysmal	278 (38.7)	53 (28.6)	
Persistent	316 (44.0)	76 (41.1)	
Permanent	124 (17.3)	56 (30.3)	
CHA_2DS_2-VASc risk score			< 0.0001
0	124 (17.3)	6 (3.2)	
1	137 (19.1)	13 (7.0)	
≥ 2	457 (63.7)	166 (89.7)	
Median (IQR)	2 (1–4)	4 (3–5)	< 0.0001
Pharmacological therapy at discharge			
VKA	614 (85.5)	140 (75.7)	0.001
Antiplatelet drug	129 (18.0)	58 (31.4)	< 0.0001

Antiarrhythmic drug	639 (89.0)	149 (80.5)	0.002
Echocardiography characteristics			
TTE variables[f]			
Left atrial area > 20 cm^2	361 (50.2)	136 (73.5)	< 0.0001
LVEF < 40%[b]	63 (8.8)	37 (20.0)	< 0.0001
TOE variables			
LASEC[g]			< 0.0001
None	407 (56.7)	61 (33.0)	
Mild	184 (25.6)	58 (31.4)	
Moderate	93 (13.0)	45 (24.3)	
Severe	34 (4.7)	21 (11.4)	
LAT	11 (1.5)	5 (2.7)	0.29
Aortic atheroma ≥ 4 mm or mobile aortic thrombus[b]	68 (9.5)	40 (21.6)	< 0.0001

Data are expressed as number (%) or mean ± standard deviation, unless otherwise indicated. AF: atrial fibrillation; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 years and Sex category (Female); IQR: interquartile range; LASEC: left atrial spontaneous echocardiographic contrast; LAT: left atrial thrombus; LVEF: left ventricular ejection fraction; TOE: transoesophageal echocardiography; TIA: transient ischaemic attack; TTE: transthoracic echocardiography; VKA: vitamin K antagonist.

[a] *P* values from univariate Cox proportional-hazards regression models.

[b] Variables included in the CHA_2DS_2-VASc risk score.

[c] Low-density lipoprotein cholesterol ≥ 4.1 mmol/L or prescription of lipid-lowering drugs or hypercholesterolaemia recorded with a date of diagnosis.

[d] Associated diagnoses on hospital admission.

[e] Recorded in the patient's history.

[f] Measurements according to American Society of Echocardiography guidelines [13, 14].

[g] Graded according to the Fatkin classification [17].

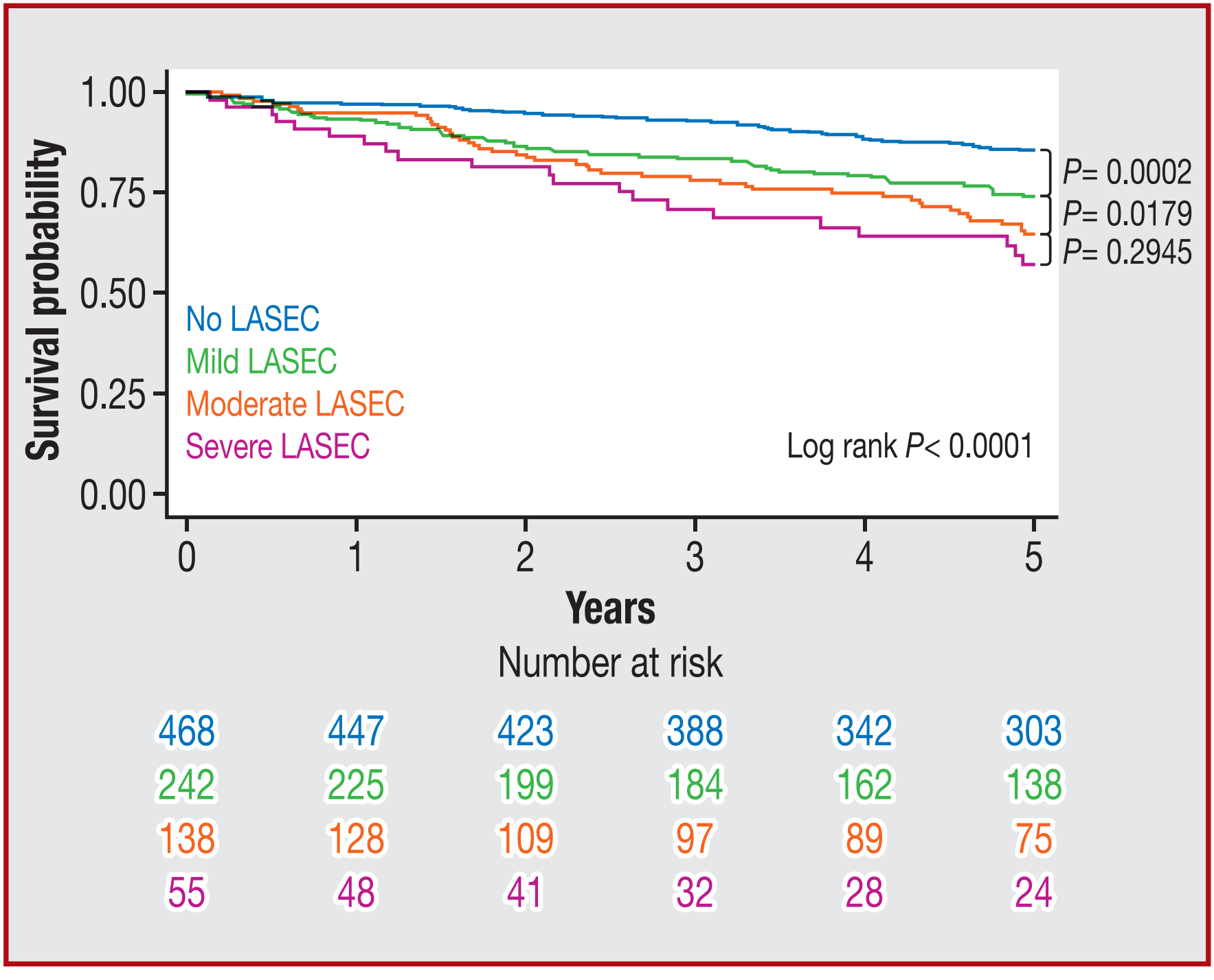
Table 2 Univariate and multivariable Cox models: Clinical and echocardiographic predictors of the composite outcome (stroke & death) at 5-year follow-up.

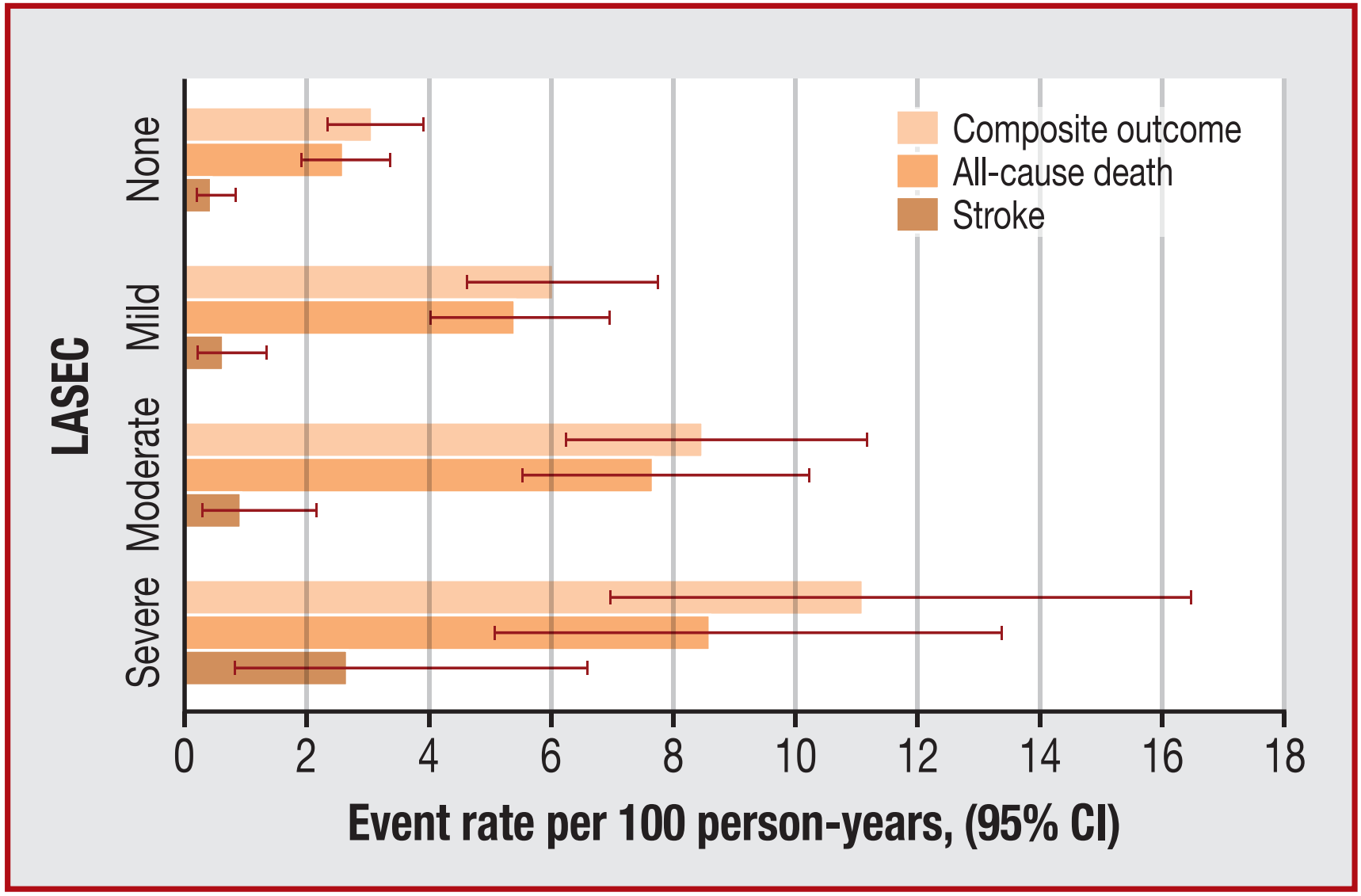
Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Clinical characteristics				
CHA_2DS_2-VASc score (per unit increase)	1.42 (1.31–1.53)	< 0.0001	1.35 (1.25–1.47)	< 0.0001
AF, persistent versus paroxysmal	1.20 (0.84–1.70)	0.32	0.94 (0.63–1.40)	0.75
AF, permanent versus paroxysmal	2.13 (1.46–3.11)	< 0.0001	0.89 (0.56–1.42)	0.63
Dyslipidaemia, yes versus no	0.69 (0.50–0.95)	0.023	0.60 (0.43–0.83)	0.002
VKA at discharge, yes versus no	0.55 (0.40–0.77)	0.001	0.68 (0.46–1.01)	0.054
Antiplatelet agents at discharge, yes versus no	1.91 (1.40–2.31)	< 0.0001	1.18 (0.82–1.70)	0.37
Antiarrhythmic drugs at discharge, yes versus no	0.56 (0.39–0.80)	0.002	0.59 (0.40–0.87)	0.008
Echocardiographic characteristics				
TTE variables				
LAA > vs ≤ 20 cm^2	2.42 (1.74–3.35)	< 0.0001	1.59 (1.08–2.35)	0.018
TOE variables				
LASEC, mild versus none[a]	1.97 (1.38–2.83)	< 0.0001	1.42 (0.98–2.09)	0.06
LASEC, moderate versus none[a]	2.76 (1.88–4.05)	< 0.0001	1.72 (1.13–2.62)	0.012
LASEC, severe versus none[a]	3.62 (2.21–5.95)	< 0.0001	2.04 (1.16–3.58)	0.013

AF: atrial fibrillation; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age

65–74 years and Sex category (Female); CI: confidence interval; HR: hazard ratio; LASEC: left atrial spontaneous echocardiographic contrast; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography; VKA: vitamin K antagonist.

[a] Graded according to the Fatkin classification [17].


Survival probability
1.00
0.75
0.50
0.25
0.00
No LASEC
Mild LASEC
Moderate LASEC
Severe LASEC
Log rank P< 0.0001
P= 0.0002
P= 0.0179
P= 0.2945
0
1
2
3
4
5
Years
Number at risk
468 447 423 388 342 303
242 225 199 184 162 138
138 128 109 97 89 75
55 48 41 32 28 24


LASEC
None
Mild
Moderate
Severe
Composite outcome
All-cause death
Stroke
0
2
4
6
8
10
12
14
16
18
Event rate per 100 person-years, (95% CI)