Received: 7 May 2021 | Accepted: 5 August 2021

DOI: 10.1111/ijcp.14706

ORIGINAL PAPER

Cardiovascular medicine

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

# Proposal for a clinical and an echocardiographic score for prediction of left atrial thrombosis in atrial fibrillation patients undergoing early electrical cardioversion

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**Funding information**
Open Access Funding provided by Universita degli Studi di Milano-Bicocca within the CRUI-CARE Agreement.
WOA Institution: Universita degli Studi di Milano-Bicocca.
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## Abstract

**Aims:** Left atrial thrombosis (LAT) is usually detected by transesophageal echocardiography (TEE). The aim of the present study was to identify clinical and echocardiographic factors associated with left atrial thrombosis in atrial fibrillation (AF) patients undergoing early electrical cardioversion (ECV) in order to create scores that can predict LAT, in a non-invasive way.

**Methods:** A consecutive cohort of patients with persistent AF scheduled for ECV was evaluated by transthoracic echocardiography and TEE. By a logistic regression model, variables significantly associated with LAT were assessed and introduced in predictive models to develop both a clinical and an echocardiographic prediction score for the presence of LAT.

**Results:** In total, 125 patients [median 71 (range 49-88) years, 60.0% males] were enrolled. Transesophageal echocardiography showed LAT in 35 patients (28%). The clinical variables significantly associated with LAT were previous stroke (OR = 4.17), higher $CHA_2DS_2$-VASc score (OR = 1.93), lower estimated glomerular filtration rate (OR = 0.80), and higher brain natriuretic peptide levels (OR = 1.44). Among echocardiographic parameters, E/e′ ratio was directly associated with LAT (OR = 2.25), while an inverse correlation was detected with left ventricular ejection fraction (OR = 0.43) and total global left atrial strain (OR = 0.59). Two prediction scores (clinical and echocardiographic) were developed. The positive predictive values of the clinical and the echocardiographic score were 80% and 100%, respectively, while the negative predictive values were 98% and 94%, respectively. Combined use of the scores reached a positive and negative predictive value of 100%.

**Conclusions:** When providing concordant information the two scores are able to correctly identify patients with or without LAT. An external validation is necessary to demonstrate their usefulness in the clinical practice.

## 1 | INTRODUCTION

Atrial fibrillation (AF) is known to increase the risk of left atrial thrombosis (LAT), and consequently of cerebral and systemic thromboembolic episodes.[1,2]

Thromboembolic risk is classically evaluated according to clinical variables included into the $CHA_2DS_2$-VASc Risk Score.[3] Thrombus formation, however, is a complex phenomenon, and involves haemoreological, tissue and humoral factors, according to the classic Virchow triad.[4,5]

The presence of thrombi and/or prethrombotic phenomena -such as high degree spontaneous echo contrast (SEC)- in the left atrial (LA) has been associated with several clinical and humoral factors.[6,7] Thrombotic phenomena are also associated with parameters assessed by two-dimensional (2D) transthoracic echocardiography (TTE)[8,9] and 2D-speckle tracking echocardiography (STE).[10,11] It has previously been shown that STE, as an implementation of standard TTE, may allow a more complete analysis of LA function, thus providing additional diagnostic and prognostic information on the pro-thrombotic state of the LA. Several studies have shown that an impaired LA deformation could effectively predict LAAT in AF patients.[12-14] Many of these parameters show a wide variability in AF patients, mainly due to the presence of the arrhythmia at the time of performing the ultrasound examination.

Transesophageal echocardiography (TEE) is the gold standard for the detection of thrombi in the LA, which most commonly form in the left atrial appendage (LAA).[15-17] Even if the conventional treatment strategy for AF patients who are to undergo ECV is to prescribe anticoagulation for three weeks before the procedure, it has been proposed that if TEE reveals no atrial thrombus, ECV may be performed safely after a shorter period.[18] However, there are some clinical scenarios in which invasive examinations should be minimised to protect both patients and healthcare professionals, performing them only when absolutely necessary.[19]

The main purpose of the present study was to non-invasively identify the clinical and echocardiographic profile of AF patients with the greatest probability of having LAT, to develop a risk prediction model that may be useful to the cardiologist in the management of NVAF patients candidate to early electrical cardioversion (ECV). To this aim, two clusters of clinical and echocardiography variables associated with LAT presence in a population of patients with persistent AF were used to create two different thrombosis risk stratification scores.

**What's known?**

- Guidelines state that electrical or pharmacological cardioversion should be performed after at least three weeks of therapeutic oral anticoagulation to prevent the risk of thromboembolism in atrial fibrillation patients.
- Electrical cardioversion can also be performed after shorter periods of anticoagulation if the execution of a transesophageal ultrasound excludes the presence of left atrial thrombosis.

**What's new?**

- Using non-invasive clinical and echocardiographic parameters, we have created two scores that are effective in identifying the presence of atrial thrombosis in atrial fibrillation patients scheduled for electrical cardioversion.
- The negative and positive predictive power of the two scores, when used together, is 100%.
- In patients with particularly low thromboembolic risk according to the scores, performing transesophageal ultrasound before cardioversion could be avoided .

## 2 | METHODS

All patients with persistent AF of ≥48 hours or of unknown duration, referred to our Echo Laboratory between April 2016 and January 2020 for a TEE examination to evaluate the presence of LAT before early ECV, were consecutively enrolled in this study.

Non-valvular AF was defined according to the 2016 ESC Guidelines.[20] Main exclusion criteria were: AF duration <48 hours, significant valvular heart disease (prosthetic valve, severe mitral valve regurgitation and more than mild mitral valve stenosis), technical inability to perform either TEE or STE analysis (ie, inappropriate endocardial border definition of both LA and LAA). The following patient information was obtained: age, gender, presence of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking), history of coronary artery disease (CAD), previous stroke/transient ischaemic attack (TIA), presence of chronic obstructive pulmonary disease, estimated glomerular filtration rate (eGFR),[21] plasma levels of N-terminal pro-B type natriuretic peptide (NT-proBNP) and oral antithrombotic treatment.

The thromboembolic risk of each patient was assessed by the $CHA_2DS_2$-VASc Risk Score.[3]

All study procedures were performed in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study is based on a retrospective analysis of examinations already performed, justified by good clinical practice and was approved by our local ethics committee All patients had signed an informed consent for the execution of transesophageal ultrasound and for the management of their data.

### 2.1 | Echocardiography examination

During the same day, before ECV, all patients underwent conventional two-dimensional (2D)-TTE implemented with 2D-STE analysis of both LA and LAA.

All echocardiographic examinations were performed by the same cardiologist (AS) with a Philips Sparq ultrasound machine (Philips Healthcare, Andover, Massachusetts, USA) by using a 2.5 mHz transducer for transthoracic examination and a 5 mHz multiplane transducer for transesophageal examination, respectively.

Echocardiographic measurements were done for five consecutive beats and thereafter averaged. All measurements were carried out according to the criteria of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[22-24]

The following echo-Doppler variables were collected: left ventricular mass index (LVMi) determined by the Devereux formula, left atrial volume index (LAVi) and left ventricular ejection fraction (LVEF) measured by the biplane modified Simpson's method, LV diastolic function assessed by the average E/e′ ratio,[23] and systolic pulmonary artery pressure (SPAP) derived by the modified Bernoulli formula.

Immediately after conventional echocardiography, during the same examination, two-dimensional STE was performed by using the Philips QLAB 10.3.1 ultrasound software (Philips Healthcare, Andover, Massachusetts, USA). Afterwards, all acquired images were analysed offline. To calculate LA strain, the software divided the LA into seven segments and a "biplane method" was used (the apical 3-chamber view was excluded because the values of the antero-septal wall correspond to the ascending aorta). After obtaining the longitudinal atrial strain curves, the following parameters were collected (Figure S1): peak positive and peak negative strain and peak-to-peak strain, that is, total global atrial strain (TGSA). The latter variable was calculated by separately averaging values observed in 4- and 2-chamber apical views. The STE results were estimated using the ratio of preceding (RR1) to pre-preceding (RR2) RR interval, employing the index-beat method.[25]

The LAA was visualised by TEE from the mid-esophageal position at 45°-90°. On average, five cardiac cycles were recorded with both the 2D and the pulsed-wave (PW) Doppler technique. LAT was defined by (a) the presence of a thrombus in the LAA (LAAT), defined as an echo-dense mass of more than 2 mm in diameter attached to the LAA wall that could clearly be distinguished from the surrounding endocardium or pectinate muscles[26] or (b) the presence of dense SEC, defined as an echogenic swirling pattern of blood flow in the LA or the LAA, distinct from white noise artifacts caused by excessive gain.[27] The intensity of SEC was graded on the basis to the classification (1 to 4) proposed by Fatkin et al.[28] Dense SEC was defined as grade 4. All images were recorded on hard disk for subsequent offline analysis.

Left atrial appendage emptying and filling velocities were measured by placing the pulsed wave sample-volume in the proximal one-third segment of the LAA with suitable gain and filter adjustments.[29]

## 2.2 | Statistical analysis

Baseline covariate distributions were summarised using descriptive statistics (median and range for continuous variables, and frequencies for categorical variables). A logistic regression model was used to develop and internally validate the predictive models of left atrial thrombosis. Those factors that were statistically associated to left atrial thrombosis in univariate analysis (ie, *P*-value ≤ .05) were introduced in different predictive models based on their classification (ie, clinical or echocardiographic predictors). The *rcs()* e *ANOVA()* functions of the 'rms' package in R were used to evaluate the linearity assumption of the logistic regression model. In order to control overfitting, if more than four predictors were introduced in regression models, the penalised likelihood estimation procedure instead of the maximum likelihood estimation procedure was used to estimate regression parameters. The Akaike's information criterion (AIC) was used to choose the penalty factor (ie, the penalty factor was chosen as the value that maximised AIC[30]). Receiver operating characteristic (ROC) curves and the area under the receiver operating curves (AUC) were used to estimate the diagnostic ability of risk prediction models. Calibration plots and the maximum error in predicting LAT probability by the calibration curve were used to estimate the agreement between future predicted probabilities and observed probabilities. The *validate()* and *calibrate()* functions of the "rms" package in R were used to internally validate risk prediction models; bootstrap was performed with 1000 resamples.

The *rpart()* function of the "rpart" package in R was used to identify the best thresholds for continuous predictive scores. After the classification tree was generated, the *prune()* function of the "rpart" package in R was used to avoid overfitting the data. The complexity parameter associated with the smallest cross-validated error was selected to optimally prune the tree. Statistical analysis was performed using the R software version 3.5.0 (2018-04-23)—R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

## 3 | RESULTS

We retrospectively evaluated 125 consecutive NVAF patients [median 71 (range 49-88) years, 75 (60.0%) males] who underwent TEE before ECV. Grade 4 SEC was detected in 15 patients (12.0%), while LAAT was diagnosed in 20 patients (16.0%). The remaining 90 patients (72.0%) did not have LAT, according to previously established criteria. Left atrial appendage emptying and filling velocities were both higher in patients without LAT compared with those with LAT [58.0 (27-79) vs 24.0 (15-34) cm/s and 52.0 (26-80) vs 26.0 (15-36) cm/s, OR: 0.59 95%CI: 0.45-0.77 and OR: 0.79 95%CI: 0.71-0.88, respectively; $P < .0001$].

Demographic, clinical and echocardiographic characteristics of the study population are shown in Table 1. There was a significant association between previous stroke (Odds Ratio, OR: 4.17 95%CI: 1.60-10.89), higher $CHA_2DS_2$-VASc score (OR: 1.93 95%CI: 1.34-2.77), lower eGFR (OR: 0.80 95%CI: 0.66-0.96, for each 10 mL/min/1.73 $m^2$ reduction) and higher NT-pro-BNP

**TABLE 1** Variables associated with the presence of left atrial thrombosis by univariate logistic regression analysis

| | | Left atrial thrombosis | | | Statistical association | | |
|---|---|---|---|---|---|---|---|
| | | Overall (N = 125) | Yes (N = 35) | No (N = 90) | OR | 95% CI | *P*-value |
| *Clinical variables* | | | | | | | |
| Age[a](years) | Median | 71 | 74 | 71 | 1.33 | 0.79-2.23 | .29 |
| | Min-max | 49-88 | 49-88 | 53-85 | | | |
| Gender | Female N (%) | 50 (40.0) | 16 (45.7) | 34 (37.8) | 1.39 | 0.63-3.06 | .42 |
| | Male N (%) | 75 (60.0) | 19 (54.3) | 56 (62.2) | 1 | | |
| Hypertension | Yes | 86 (68.8) | 26 (74.3) | 60 (66.7) | 1.44 | 0.60-3.47 | .41 |
| | No | 39 (31.2) | 9 (25.7) | 30 (33.3) | 1 | | |
| Smoking | Yes | 42 (33.6) | 12 (34.3) | 30 (33.3) | 1.04 | 0.46-2.38 | .92 |
| | No | 83 (66.4) | 23 (65.7) | 60 (66.7) | 1 | | |
| Type 2 diabetes mellitus | Yes | 31 (24.8) | 11 (31.4) | 20 (22.2) | 1.60 | 0.67-3.83 | .29 |
| | No | 94 (75.2) | 24 (68.6) | 70 (77.8) | 1 | | |
| Dyslipidemia | Yes | 69 (55.2) | 21 (60.0) | 48 (53.3) | 1.31 | 0.59-2.90 | .50 |
| | No | 56 (44.8) | 14 (40.0) | 42 (46.7) | 1 | | |
| History of CAD | Yes | 30 (24.0) | 5 (14.3) | 25 (27.8) | 0.43 | 0.15-1.24 | .12 |
| | No | 95 (76.0) | 30 (85.7) | 65 (72.2) | 1 | | |
| Prior cardiac surgery | Yes | 26 (20.8) | 6 (17.1) | 20 (22.2) | 0.72 | 0.26-1.99 | .53 |
| | No | 99 (79.2) | 29 (82.9) | 70 (77.8) | 1 | | |
| Previous TIA/stroke | Yes | 22 (17.6) | 12 (34.3) | 10 (11.1) | 4.17 | 1.60-10.9 | **.003** |
| | No | 103 (82.4) | 23 (65.7) | 80 (88.9) | 1 | | |
| COPD | Yes | 35 (28.0) | 10 (28.6) | 25 (27.8) | 1.04 | 0.44-2.47 | .93 |
| | No | 90 (72.0) | 25 (71.4) | 65 (72.2) | 1 | | |
| $CHA_2DS_2$-VASc Risk Score | 1-2 | 17 (13.6) | 2 (5.7) | 15 (16.7) | 1.93 | 1.34-2.77 | **<.0001** |
| | 3 | 34 (27.2) | 4 (11.4) | 30 (33.3) | | | |
| | 4 | 40 (32.0) | 12 (34.3) | 28 (31.1) | | | |
| | 5 | 23 (18.4) | 10 (28.6) | 13 (14.4) | | | |
| | 6-7 | 11 (8.8) | 7 (20.0) | 4 (4.4) | | | |
| eGFR (mL/min/1.73 $m^2$)[a] | Median | 74.0 | 63.2 | 80.3 | 0.80 | 0.66-0.96 | **.018** |
| | Min-max | 21.5-142.0 | 21.5-142.0 | 34.8-124.3 | | | |
| NT-proBNP (pg/mL)[b] | Median | 170.0 | 862.0 | 111.5 | 1.44 | 1.27-1.63 | **<.0001** |
| | Min-max | 75-2100 | 425-2100 | 75-1600 | | | |
| Serum potassium (mEq/L) | Median | 4.1 | 4.1 | 4.2 | 0.57 | 0.21-1.50 | .25 |
| | Min-max | 3.2- 5.8 | 3.6-4.8 | 3.2-5.8 | | | |
| VKAs | Yes | 32 (25.6) | 8 (22.9) | 24 (26.7) | 0.81 | 0.33-2.04 | .66 |
| | No | 93 (74.4) | 27 (77.1) | 66 (73.3) | 1 | | |
| NOACs | Yes | 93 (74.4) | 27 (77.1) | 66 (73.3) | 1.23 | 0.49-3.07 | .66 |
| | No | 32 (25.6) | 8 (22.9) | 24 (26.7) | 1 | | |
| Antiplatelets | Yes | 23 (18.4) | 4 (11.4) | 19 (21.1) | 0.48 | 0.15-1.53 | .22 |
| | No | 102 (81.6) | 31 (88.6) | 71 (78.9) | 1 | | |
| *Echocardiographic variables* | | | | | | | |
| LVMi ($g/m^2$)[a] | Median | 97 | 94 | 97 | 1.03 | 0.90-1.17 | .68 |
| | Min-max | 50-185 | 55-185 | 50-172 | | | |
| LVEF (%)[a] | Median | 57 | 50 | 58 | 0.43 | 0.29-0.64 | **<.0001** |
| | Min-max | 20-70 | 20-70 | 25-70 | | | |
| Average E/e′ ratio | Median | 11.3 | 18.5 | 11.0 | 2.25 | 1.64-3.10 | **<.0001** |
| | Min-max | 4.4-28.7 | 7.7-28.7 | 4.4-16.0 | | | |

(Continues)

**TABLE 1** (Continued)

| | | Left atrial thrombosis | | | Statistical association | | |
|---|---|---|---|---|---|---|---|
| | | Overall (N = 125) | Yes (N = 35) | No (N = 90) | OR | 95% CI | *P*-value |
| LAVi (mL/m$^2$)[a] | Median | 45.2 | 45.4 | 45.1 | 1.19 | 0.82-1.73 | .35 |
| | Min-max | 24.2-71.6 | 34.0-64.4 | 24.2-71.6 | | | |
| SPAP (mm Hg)[a] | Median | 36 | 37 | 36 | 1.19 | 0.85-1.65 | .31 |
| | Min-max | 21-75 | 23-70 | 21-75 | | | |
| TGSA (%) | Median | 12.0 | 8.9 | 13.6 | 0.59 | 0.47-0.74 | **<.0001** |
| | Min-max | 4.5-20.9 | 4.5-12.5 | 6.8-20.9 | | | |

*Note:* Significant *P* values are in bold.

Abbreviations: CAD, coronary artery disease; $CHA_2DS_2$-VASc, Congestive heart failure, Hypertension, Age at least 75 years (doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65-74 years, Sex category (female); CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LAAT, left atrial appendage thrombosis; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NOACs, novel oral anticoagulants; NT-pro-BNP, N-terminal pro-B type natriuretic peptide; OR, odds ratio; SPAP, systolic pulmonary artery pressure; TGSA, total global atrial strain; TIA, transient ischaemic attack; VKAs, vitamin K antagonists.

[a]Odds ratio increment: 10 units.

[b]Odds ratio increment: 100 units.

plasma levels (OR: 1.44 95%CI: 1.27-1.63, for each 100 pg/mL increase) and the presence of LAT. Among echocardiographic variables, E/e′ ratio was directly associated with LAT (OR: 2.25 95%CI: 1.64-3.10), while an inverse correlation was detected with LVEF (OR: 0.43 95%CI: 0.29-0.64, for each 10 percentage points) and TGSA (OR: 0.59 95%CI: 0.47-0.74). No other clinical or echocardiographic variables were significantly associated with the presence of LAT. In particular, there were no differences that could be accounted for by the use of any specific type of antithrombotic therapy.

At multivariable analysis, the strongest clinical predictor of LAT was NT-pro-BNP (OR: 1.44 95%CI: 1.26-1.65), while LVEF (OR: 0.32 95%CI: 0.13-0.81), E/e′ (OR: 2.35 95%CI: 1.41-3.91) and TGSA (OR: 0.57 95%CI: 0.36-0.89) were all independently associated with LAT in the echocardiographic model (Table 2). Based on multivariable logistic regression, three model equations were obtained to develop three prediction scores: clinical score [model equation = −5.923 + 1.081*Stroke/TIA + 0.272*$CHA_2DS_2$-VASc − 0.236*(eGFR/10) + 1.041*min [(BNP/100);7.5)]; echocardiographic score [model equation = +0.554 − 1.138*(LVEF/10) + 0.855*E/e′ − 0.565*TGSA)] and clinical/echocardiographic score [model equation = −2.175 + 0.601*Stroke/TIA + 0.095* $CHA_2DS_2$-VASc − 0.004*(eGFR/10) + 0.235*(BNP/100) + 0.738*E/e′ − 0.468*TGSA − 0.872*(LVEF/10)]. The probability of LAT was calculated as follows: 1/[1 + exp(−score)].

The discrimination capability of the three scores is shown in Figure 1. All the scores have a good discrimination capability (clinical score: Area Under the Curve, AUC = 0.961; echocardiographic score: AUC = 0.985; clinical/echocardiographic score: AUC = 0.995). Based on the best thresholds identified by the ROC curves (clinical score threshold = ≥−0.321, echocardiographic score threshold = ≥1.596, clinical/echocardiographic score threshold = ≥−0.430), the negative predictive values (NPV) of the three scores were 98%, 94% and 98%, respectively, while the positive

**TABLE 2** Variables associated with the presence of left atrial thrombosis by multivariate logistic regression analysis

| | OR | 95% CI | *P* value |
|---|---|---|---|
| *Clinical model* | | | |
| Previous TIA/stroke | | | |
| Y vs N (ref = N) | 2.26 | 0.55-9.29 | .26 |
| $CHA_2DS_2$-VASc Risk Score | 1.58 | 0.93-2.70 | .094 |
| eGFR (mL/min/1.73 m$^2$)[a] | 0.83 | 0.65-1.06 | .14 |
| NT-proBNP (pg/mL)[b] | 1.44 | 1.26-1.65 | **<.0001** |
| *Echocardiographic model* | | | |
| LVEF (%)[a] | 0.32 | 0.13-0.81 | **.016** |
| Average E/e′ ratio | 2.35 | 1.41-3.91 | **.001** |
| TGSA (%) | 0.57 | 0.36-0.89 | **.014** |
| *Clinical/echocardiographic model* | | | |
| Previous TIA/stroke | | | |
| Y vs N (ref = N) | 1.82 | 0.10-33.96 | .69 |
| $CHA_2DS_2$-VASc Risk Score | 1.22 | 0.43-3.49 | .71 |
| eGFR (mL/min/m$^2$)[a] | 1.06 | 0.55-2.07 | .86 |
| NT-proBNP (pg/mL)[b] | 1.30 | 1.04-1.62 | **.022** |
| LVEF (%)[a] | 0.36 | 0.13-1.00 | .050 |
| Average E/e′ ratio | 2.54 | 1.28-5.04 | **.008** |
| TGSA (%) | 0.56 | 0.33-0.95 | **.030** |

*Note:* Significant *P* values are in bold.

Abbreviations: $CHA_2DS_2$-VASc, Congestive heart failure, Hypertension, Age at least 75 years (doubled), Diabetes, Stroke/transient ischemic attack/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65-74 years, Sex category (female); CI, confidence interval; eGFR, estimated glomerular filtration rate; LAAT, left atrial appendage thrombosis; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B type natriuretic peptide; OR, odds ratio; TGSA, total global atrial strain; TIA, transient ischemic attack.

[a]Odds ratio increment: 10 units.

[b]Odds ratio increment: 100 units.

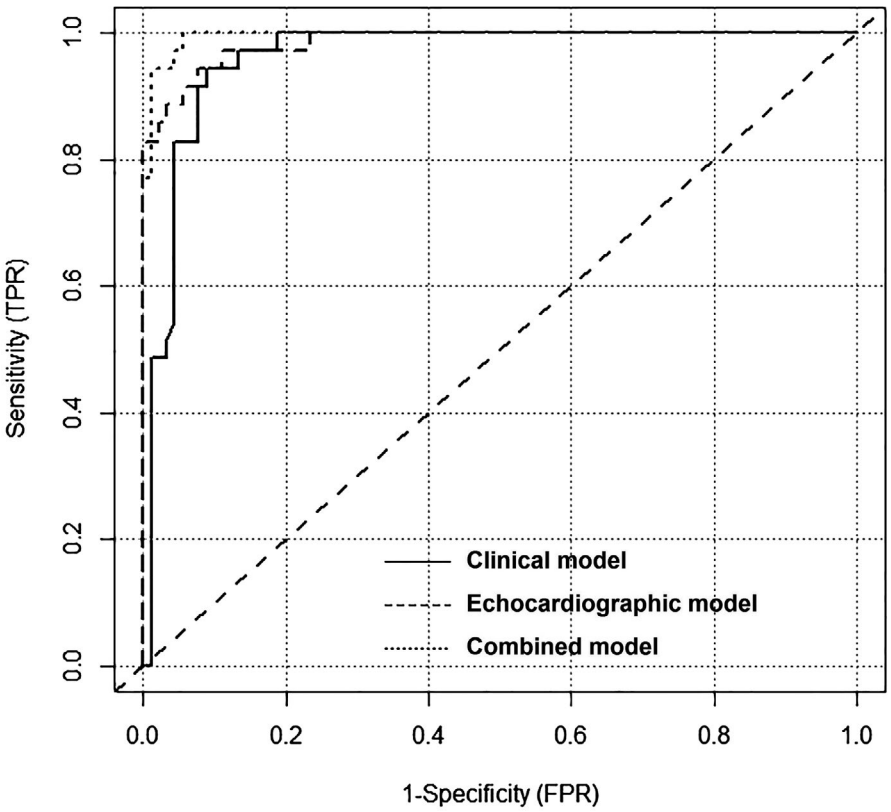


**FIGURE 1** Receiver operating characteristic (ROC) curve for clinical, echocardiographic and clinical/echocardiographic scores. Clinical score threshold = ≥−0.321, echocardiographic score threshold = ≥1.596, clinical/echocardiographic score threshold = ≥−0.430

predictive values (PPV) were 80%, 100% and 97%, respectively. The clinical score showed a specificity of 91% and a sensitivity of 94%, the echocardiography score a specificity of 100% and a sensitivity of 83%, and the clinical/echocardiographic score a specificity of 99% and a sensitivity of 94% (Table 3).

After internal validation, all the scores confirmed a good discrimination capability (clinical score: Area Under the Curve, AUC = 0.955; echocardiographic score: AUC = 0.979; clinical/echocardiographic score: AUC = 0.984), while only clinical and echocardiographic score showed a good calibration capability (maximum error in predicting LAT probability by the estimated calibration curve = 0.056 and 0.041, respectively). The clinical/echocardiographic score showed an excessively high maximum error = 0.183, due to the small number of patients showing LAT (ie, the model was overfitted). Calibration plots are shown in Figure S2.

The discrimination capability of the $CHA_2DS_2$-VASc score in identifying patients with LAT was also evaluated. The $CHA_2DS_2$-VASc had a moderate discrimination capability, inferior to the new three scores (AUC = 0.714; 95%CI: 0.614-0.813, Figure S3).

Figure 2 show the graphic representation of the clinical and echocardiographic scores and of the probability of LAT. The patient's clinical and echocardiographic scores can be simply calculated by inserting the values of the patient's variables in the nomogram, finding the relative "point" (from 0 to 100) for each variable and adding up the results of the individual items.

**TABLE 3** Predictive capability of clinical, echocardiographic and clinical/echocardiographic scores

| **Clinical model (threshold ≥−0.321)** | **Specificity (91%)** | **Sensitivity (94%)** |
|---|---|---|
| NPV (98%) | 82 TN | 2 FN |
| PPV (80%) | 8 FP | 33 TP |
| **Echocardiographic model (threshold ≥1.596)** | **Specificity (100%)** | **Sensitivity (83%)** |
| NPV (94%) | 90 TN | 6 FN |
| PPV (100%) | 0 FP | 29 TP |
| **Clinical/echocardiographic (threshold ≥−0.430)** | **Specificity (99%)** | **Sensitivity (94%)** |
| NPV (98%) | 89 TN | 2 FN |
| PPV (97%) | 1 FP | 33 TP |

Abbreviations: FN, false negative, FP, false positive. NPV, negative predictive value. PPV, positive predictive value. TN, true negative. TP, true positive.

The combined use of the two scores allowed to reach a negative predictive value and a positive predictive value both of 100%, correctly identifying (with or without LAT) 109 out of 125 patients (Table 4). Both scores identify as having LAT 27 patients and in 16 patients they gave a discordant result (Table 4).

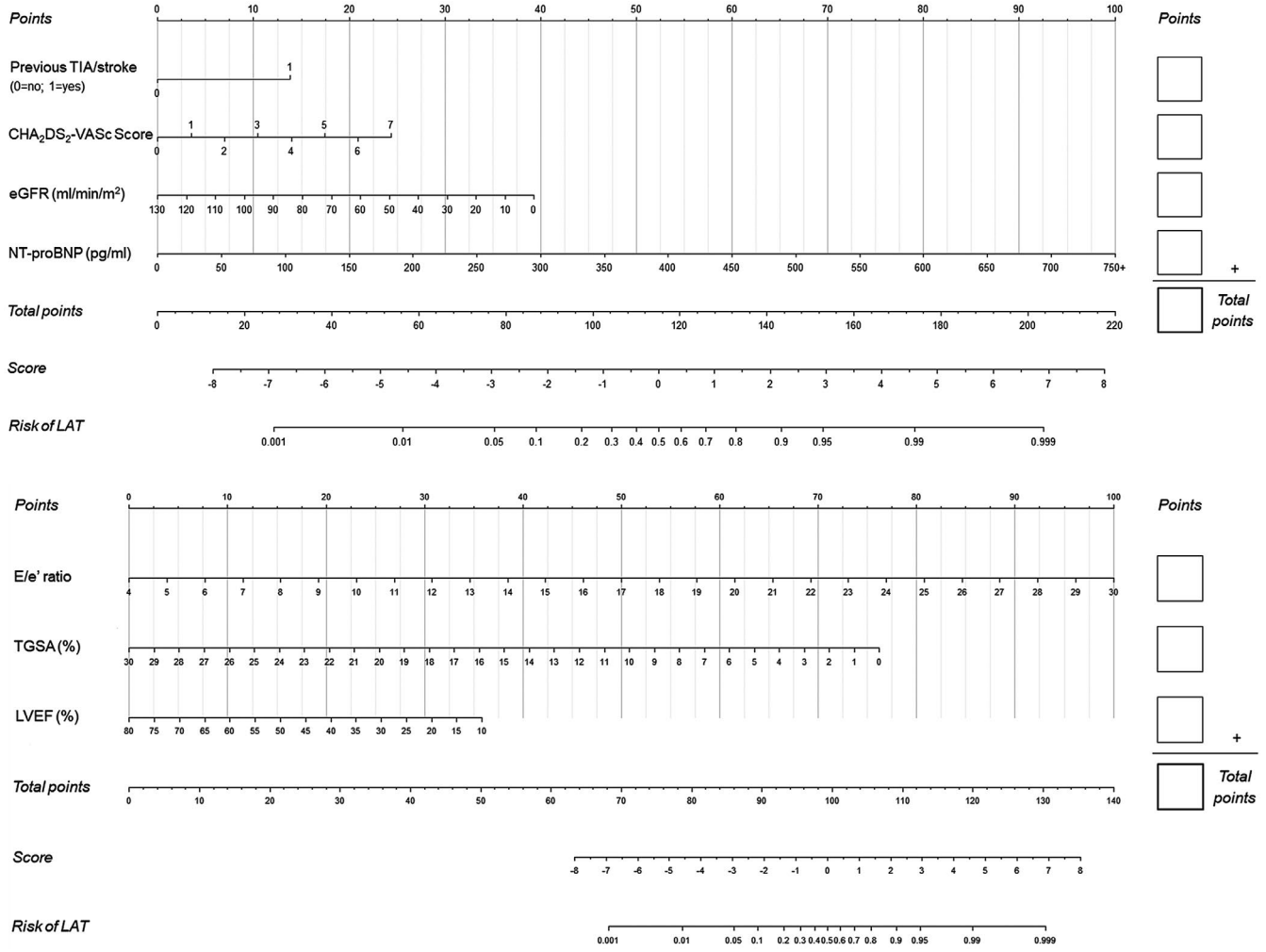


**FIGURE 2** Clinical nomogram (Upper Panel) and echocardiographic nomogram (Bottom Panel) calculating score and probability for left atrial thrombosis. For each predictor, read the points assigned on the "Points" axis. The sum of all points can be referred to the total points axis. Then the score (ie, the linear predictor on log scale) and the probability of left atrial thrombosis can be obtained. $CHA_2DS_2$-VASc, **C**ongestive heart failure, **H**ypertension, **A**ge at least 75 years (doubled), **D**iabetes, **S**troke/transient ischemic attack/thromboembolism (doubled), **V**ascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), **A**ge 65-74 years, **S**ex category (female); eGFR, estimated glomerular filtration rate; LAT, left atrial thrombosis; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; TGSA, total global atrial strain; TIA, transient ischemic attack

## 4 | DISCUSSION

In patients that are a candidate for electrical cardioversion, it is important to be able to predict the presence of thrombotic formations in the left atrium/left appendage or of spontaneous high-grade echo contrast, as these situations contraindicate cardioversion.

Our study suggests the usefulness of two scores, one clinical and the other echocardiographic, to predict the presence/absence of atrial thrombosis or spontaneous echo contrast in patients with atrial fibrillation in need of electrical cardioversion. The scores were created on the basis of factors that were significantly associated with the presence of atrial thrombosis or spontaneous echo contrast, as detected by transesophageal echocardiography. Among the clinical parameters, the $CHA_2DS_2$-VASc score and the NT-pro-BNP value showed a direct correlation with the presence of atrial thrombosis, whereas eGFR was inversely correlated. A history of previous stroke or TIA was associated with an increased risk of atrial thrombosis. The echocardiographic parameters predicting atrial thrombosis or echo contrast were a lower left ventricular ejection fraction, a higher E/e′ ratio, and a lower left atrial strain value.

When electrical cardioversion is about to be performed, the crucial point is to decide in which patients it is essential to perform transesophageal echocardiography, especially if anticoagulation therapy had started less than three weeks before. Both the clinical and the echocardiographic score we propose show high sensitivity and specificity and respond positively to internal validation. In this clinical context, the usefulness of a score is not so much that of identifying patients who certainly have atrial thrombosis, but those who certainly do not. For this purpose, neither one nor the other score proposed by us can be considered sufficiently effective,

**TABLE 4** Predictive capability of combined use of clinical and echocardiographic score

| Clinical score | Echocardiographic score | Thrombosis NO | Thrombosis YES | NPV | PPV |
|---|---|---|---|---|---|
| Thrombosis NO | Thrombosis NO | 82 | 0 | 100% | – |
| Thrombosis YES | Thrombosis NO | 8 | 6 | 57% | 43% |
| Thrombosis NO | Thrombosis YES | 0 | 2 | – | 100% |
| Thrombosis YES | Thrombosis YES | 0 | 27 | – | 100% |

Abbreviations: NPV, negative predictive value. PPV, positive predictive value.

if used individually. The echocardiographic score, despite having a positive predictive value of 100% (correctly identifying all patients with thrombosis), has a negative predictive value of 93%. This means that, in our population, it did not identify 6 out of 96 patients, who, if subjected to electrical cardioversion, could have a thromboembolic event. This obviously represents an unacceptable percentage. The clinical score, which has a better negative predictivity (negative predictive value 98%), would classify 8 out of 41 patients who do not have atrial thrombosis (positive predictive value 80%) as candidates for the transesophageal ultrasound. However, the combined use of both scores allows us to achieve a positive and negative predictive power of 100% in the case of a concordant result.

The cardiology Guidelines[31,32] state that electrical or pharmacological cardioversion should be performed after at least three weeks of therapeutic oral anticoagulation. Electrical cardioversion can also be performed after shorter periods of anticoagulation in patients taking VKA inhibitors or oral direct anticoagulants if the execution of a transesophageal ultrasound excludes the presence of thrombi. In the presence of uncertainty about the patient's level of anticoagulation, many centers still perform transesophageal echocardiography before all cardioversions.

The presence of left atrial appendage thrombosis during nonvalvular atrial fibrillation has been associated with several clinical[33-35] and echocardiographic[8,9,36] variables. The $CHA_2DS_2$-VASc score, based on clinical risk factors, demonstrated a strong association with the incidence of thrombo-embolic events. Our study suggests that the integration of clinical and echocardiographic parameters may better identify patients at risk of thromboembolism than the only use of the $CHA_2DS_2$-VASc score. It should be emphasised that the presence of atrial thrombosis is not synonymous with thrombo-embolic events. Furthermore, our scores identify the probability of atrial thrombosis regardless of the duration of the anticoagulant therapy, which could be taken even for a limited time in the case of an accelerated cardioversion procedure.[18,31,32]

In our series the prevalence of high-grade echo contrast and/or LAAT was 28%, a high value compared with those reported in the literature.[37] A possible cause could be that, in our study, even patients with high-grade spontaneous echo contrast were considered as patients with atrial thrombosis. This particular echocardiographic finding is the result of the initial formation of fibrin bridges between red blood cells, which represents a pre-thrombotic situation, and its detection is an indication not to perform cardioversion. From the point of view of clinical behavior, a high-grade spontaneous echo contrast is then managed as the presence of atrial thrombosis. Another reason for the observed high prevalence of thrombosis/high-grade spontaneous echo contrast is that this study also included patients who had been taking anticoagulant therapy for a short time. It cannot be excluded that re-evaluation after three weeks or more of anticoagulation therapy could have demonstrated the disappearance of the thrombi in these patients.

A limitation of the study may be that echocardiographic parameters were acquired during atrial fibrillation. The presence of this arrhythmia could partly affect the validity of some of the parameters considered. However, we think that the evaluation of the anatomical and functional characteristics of the heart in the presence of atrial fibrillation (left ventricular ejection fraction for the evaluation of systolic function, E/e′ ratio for the evaluation of diastolic function, atrial strain for the evaluation of the mechanical properties of the left atrium) may be essential to identify the determinants for thrombus formation. The atrial strain calculation was carried out with a software developed for the evaluation of the ventricular strain, whereas this parameter is usually performed in sinus rhythm patients. However, left atrial strain assessment by 2D-STE in NVAF patients has already been validated.[38-40] Atrial contractility, particularly in the reservoir phase, is not equally depressed in all patients with atrial fibrillation, and its reduction is likely related to the degree of atrial remodeling of the individual patient. Our results revealed that atrial strain was moderately reduced in atrial fibrillation patients without LAT (13.6%) and significantly reduced in atrial fibrillation patients with LAT (8.9%) in comparison to the accepted normal ranges.[41,42] In other words, the mechanical properties of the left atrium were reduced due the presence of atrial fibrillation, but they were further impaired in patients with co-existing atrial fibrillation and left atrial thrombosis. The present study is a retrospective one and data on 3D Echography and computed tomography (CT) scan were not available. It is likely that 3D Echography would have provided a more detailed assessment of LAA morphology, however, this methodology is not available at our Echocardiography Laboratory. Finally, even if American Society of Echocardiography Guidelines suggest to perform an alternative imaging modality such as contrast-enhanced CT for the exclusion of LAAT before electrical cardioversion,[43] this examination has the following limitations: variable waiting lists and waiting times among different Institutions, the risk of transporting a patient through the hospital to the CT scanner, the need to disinfect the CT room, the administration of iodinated contrast and possible claustrophobia.

## 5 | CONCLUSION

In non-valvular atrial fibrillation patients selected for early electrical cardioversion a complete clinical and laboratory evaluation combined with an assessment of left ventricular systolic and diastolic function and left atrial mechanical properties could be important to quantify the risk of left atrial thrombosis and should be implemented in the clinical practice. Our study proposes two scores, created by using easily detectable clinical and echocardiographic parameters, which, if used together, seem to satisfactorily identify patients with atrial thrombosis who, if subjected to electrical cardioversion, would be at high risk of stroke or peripheral thromboembolism. The study allowed only internal validation of the scores and an external validation in a larger cohort of patients with atrial fibrillation is required to understand the real usefulness of these scores in identifying patients without atrial thrombosis, who could undergo cardioversion without performing a transesophageal echocardiogram. Our scores were created with the aim of identifying, among patients who are candidates for a rhythm control strategy, those at low risk of LAT to help the cardiologist to decide if a TEE may be avoided. For this reason, they cannot be generalised to the whole AF population. However, they could be useful also in patients for whom a rate control strategy has been planned, for a thromboembolic risk stratification.

## 6 | ETHICAL STANDARD

The study was approved by our local ethics committee and was carried out in accordance with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki.

## 7 | INFORMED CONSENT

The study is based on a retrospective analysis of examinations already performed, justified by good clinical practice. All patients have signed an informed consent for the execution of transesophageal ultrasound and for the management of their data.

### DISCLOSURES

We disclose any conflict of interest, including specific financial interests and relationships and affiliations relevant to the subject.

### AUTHOR CONTRIBUTIONS

SG and AV conceptualised and designed the study. AS, SG and AV drafted the initial manuscript, and reviewed and revised the manuscript. AS collected data. LP performed data analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Vincenti A, Porcu L, Sonaglioni A, Genovesi S. Proposal for a clinical and an echocardiographic score for prediction of left atrial thrombosis in atrial fibrillation patients undergoing early electrical cardioversion. *Int J Clin Pract*. 2021;75:e14706. https://doi.org/10.1111/ijcp.14706