CLOTS-AF Score: un punteggio per identificare i pazienti ad alto rischio di trombosi dell'auricola sinistra in previsione di cardioversione

Background

- Atrial fibrillation (AF) is associated with a 5-fold increased risk of stroke and thromboembolism.
- Left atrial appendage thrombus (LAAT) is a common source of emboli and has been implicated in up to 90% of AF-related strokes.
- To minimize the risk of thromboembolism, guideline-directed anticoagulation is required for 3 weeks before direct cardioversion (DCR) or a preprocedural transesophageal echocardiogram (TEE) is recommended to facilitate an expedited cardioversion.
- LAAT is present in up to 2.7% of patients with AF/atrial flutter (AFL) despite guideline-directed anticoagulation and in up to 23% of patients with inadequate anticoagulation.

J Am Heart Assoc. 2023;12:e029259.

Background

- Therefore, identifying patients with a high probability of LAAT and selecting a suitable period of therapeutic anticoagulation rather than early TEE-guided DCR, may minimize the procedural risk to the patient and promote better health care usage by reducing cost and resources associated with TEE.
- The CHA_2DS_2VASc score has been widely adopted to predict stroke risk among the AF population, although the predictive value of 0.67 is relatively modest.
- Prior studies have demonstrated a modest predictive value for the CHA_2DS_2VASc score in determining the presence of LAAT.

J Am Heart Assoc. 2023;12:e029259.

ORIGINAL RESEARCH

Identifying Patients at High Risk of Left Atrial Appendage Thrombus Before Cardioversion: The CLOTS-AF Score

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J Am Heart Assoc. 2023;12:e029259.

Aim of the study

The aim of the study was to identify noninvasive clinical and echocardiographic predictors of LAAT and dense spontaneous echo contrast (SEC) in a large population of consecutive patients with AF/AFL undergoing TEE in whom guideline-directed anticoagulation recommendations were not satisfied.

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Methods

- Clinical and transthoracic echocardiographic parameters were evaluated to predict LAAT risk in consecutive patients with AF/AFL undergoing TEE before cardioversion between 2002 and 2022.
- Patients referred for TEE on the basis of inadequate anticoagulation or subtherapeutic INR were retrospectively identified from a large tertiary referral center
- Regression analysis identified predictors of LAAT were combined to create the novel CLOTS-AF risk score (comprising clinical and echocardiographic LAAT predictors), which was developed in the derivation cohort (70%) and validated in the remaining 30%.

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Methods

The rationale for a TEE-guided approach to cardioversion was attributed to the following reasons:

- an inadequate period of preprocedure systemic anticoagulation defined as <3 weeks of uninterrupted DOAC or subtherapeutic anticoagulation (INR <2 within the 4 weeks before DCR in those on warfarin) in those with AF/AFL lasting >48 hours or of unclear duration (n=611);
- documented nonadherence with systemic anticoagulation (n=208),
- no systemic anticoagulation (n=104);
- subtherapeutic anticoagulation in the setting of a reported relative contraindication (n=30);
- uncertain or undocumented reasons (n=48).

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Baseline characteristics

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1001 patients
- mean age 62±13 yrs
- 25% women
- LVEF 49.8±14%

LAAT identified in 140 patients (14%) and dense spontaneous echo contrast precluding cardioversion in a further 75 patients (7.5%)

Baseline characteristics	No LAAT (N=786)	LAAT (N=215)	*P* value
Age, y	61±13	63±13	0.15
Female, n (%)	195 (25)	57 (27)	0.60
BMI, kg/m^2	29±6	30±7	0.70
Rhythm at TEE			<0.001
AF, n (%)	519 (66)	183 (85)	<0.001
AFL, n (%)	267 (34)	32 (15)	
PsAF duration, d	118±237	216±387	0.005
Anticoagulation <30 d, n (%)	241 (57)	116 (62)	0.20
Heart failure, n (%)	205 (26)	119 (55)	<0.001
Prior MI, n (%)	122 (16)	44 (20)	0.084
Creatinine, µmol/L	91±40	108±65	<0.001
OSA, n (%)	65 (8.3)	17 (7.9)	0.90
Diabetes, n (%)	118 (15)	46 (21)	0.025
Obesity (BMI ≥30 kg/m^2)	277 (35)	79 (37)	0.70
Hypertension, n (%)	385 (49)	112 (52)	0.40
Hyperlipidemia, n (%)	255 (32)	81 (38)	0.20
Cardiac device, n (%)	52 (6.6)	36 (17)	<0.001
Stroke/TIA, n (%)	34 (4.3)	29 (13.5)	<0.001
PVD, n (%)	24 (3.1)	17 (7.9)	0.001
$CHADS_2VASc$ score, mean±SD	1.9±1.4	2.3±1.3	<0.001
$CHADS_2VASc$ score ≥2, n (%)	435 (55)	157 (73)	<0.001

Baseline characteristics

Baseline characteristics	No LAAT (N=786)	LAAT (N=215)	*P* value
Baseline pharmacotherapy			
Anticoagulant type			<0.001
Apixaban, n (%)	155 (19.7)	29 (13.5)	
Dabigatran, n (%)	37 (4.7)	5 (2.3)	
Rivaroxaban, n (%)	117 (15)	23 (10.7)	
Warfarin, n (%)	170 (21.6)	133 (61.9)	
None, n (%)	307 (39)	25 (11.6)	
Beta blocker, n (%)	614 (78)	149 (69)	0.007
ACEi/ARB/ARNi, n (%)	398 (51)	103 (48)	0.50
Antiarrhythmics, n (%)	317 (40)	109 (51)	0.006
MRA, n (%)	96 (12)	26 (12)	0.98
Furosemide, n (%)	175 (22)	98 (46)	<0.001

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Baseline Echocardiographic Characteristics

Echocardiographic characteristics	No LAAT (N=786)	LAAT (N=215)	*P* value
TTE parameters			
SBP at TTE, mm Hg	127±18	121±18	<0.001
LVEF, %	52±14	41±14	<0.001
LV mass, g	194±60	215±74	0.001
LVEDD, mm	51±8	55±16	<0.001
E/e′	11±6	16±9	<0.001
TAPSE, cm	2.0±0.5	1.7±0.5	<0.001
RVSP, mm Hg	31±11	35±10	<0.001
LA diameter, mm	44±7	49±9	<0.001
LA area, cm^2	26±6	30±7	<0.001
LAVI, mL/m^2	43±14	55±21	<0.001
RA area, $cm/^2$	20.9±5.6	24.3±7.1	<0.001
RA volume, mL	69±38	91±33	<0.001
MR grade, n (%)			<0.001
None	576 (73)	76 (35)	
Mild	134 (17)	96 (45)	
Moderate	68 (8.7)	37 (17)	
Severe	8 (1)	6 (2.8)	
TEE parameters			
Rhythm at TEE			<0.001
AF, n (%)	515 (66)	179 (83)	
AFL, n (%)	271 (34)	36 (17)	
SBP, mm Hg	117±17	114±20	0.003
LAA velocity, cm/s	48±19	25±12	<0.001

Univariable Regression

	OR	95% CI	*P* value
Age	1.002	0.995–1.240	0.112
Female sex	0.982	0.885–1.090	0.611
BMI	1.001	0.993–1.008	0.869
Rhythm			<0.001
AF	1.107	1.061–1.150	
AFL	0.927	0.823–1.043	
PsAF duration	1.22	1.18–1.26	<0.001
Heart failure	1.333	1.218–1.459	<0.001
Hypertension	1.037	0.947–1.135	0.419
Prior MI	1.161	1.028–1.310	0.084
Diabetes	1.143	1.006–1.300	0.025
Stroke	1.359	1.112–1.661	<0.001
TIA	1.153	0.874–1.521	0.027
PVD	1.403	1.104–1.781	0.001
Creatinine	1.001	1.001–1.002	<0.001
$CHADS_2VASc$ score	1.098	1.060–1.137	<0.001
$CHADS_2VASc$ score ≥2	1.195	1.090–1.309	<0.001
Anticoagulant duration	1.02	0.922–1.130	0.182
Warfarin vs NOAC	1.51	1.340–1.699	<0.001
Rivaroxaban vs other NOAC	1.039	0.918–1.176	0.117
LVEF	0.987	0.983–0.990	<0.001
LAVI	1.007	1.004–1.009	<0.001
LVEDD	1.005	1.001–1.010	<0.001
E/e'	1.019	1.011–1.027	<0.001
LV mass	1.002	1.001–1.003	<0.001
TAPSE	0.965	0.933–0.999	<0.001
RVSP	1.014	1.008–1.020	<0.001

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Multivariable Regression

	OR	95% CI	*P* value
Clinical parameters			
AF rhythm	1.210	1.049–1.432	<0.001
PsAF duration	1.000	0.999–1.001	0.344
Diabetes	1.168	0.806–1.189	0.672
Stroke	1.432	1.089–1.881	0.002
Prior MI	0.972	0.898–1.314	0.947
PVD	1.212	0.910–1.614	0.187
Creatinine	1.002	1.001–1.003	0.019
$CHADS_2VASc$ score	1.212	0.987–1.378	0.124
Anticoagulant >30 d	0.923	0.800–1.065	0.271
Anticoagulant type			
Apixaban	0.754	0.563–1.078	0.172
Dabigatran	0.853	0.658–1.106	0.228
Rivaroxaban	0.992	0.824–1.195	0.935
Warfarin	1.173	0.994–1.383	0.059
Echocardiographic parameters			
LVEDV	1.001	0.999–1.003	0.127
LVEDD	0.997	0.985–1.009	0.075
LVEF	0.992	0.987–0.997	<0.001
E/e′	1.005	0.993–1.017	0.882
LV mass	0.999	0.998–1.001	0.623
LAVI	1.024	1.006–1.027	<0.001
TAPSE	0.904	0.753–0.977	<0.001
RVSP	1.008	0.998–1.015	0.424

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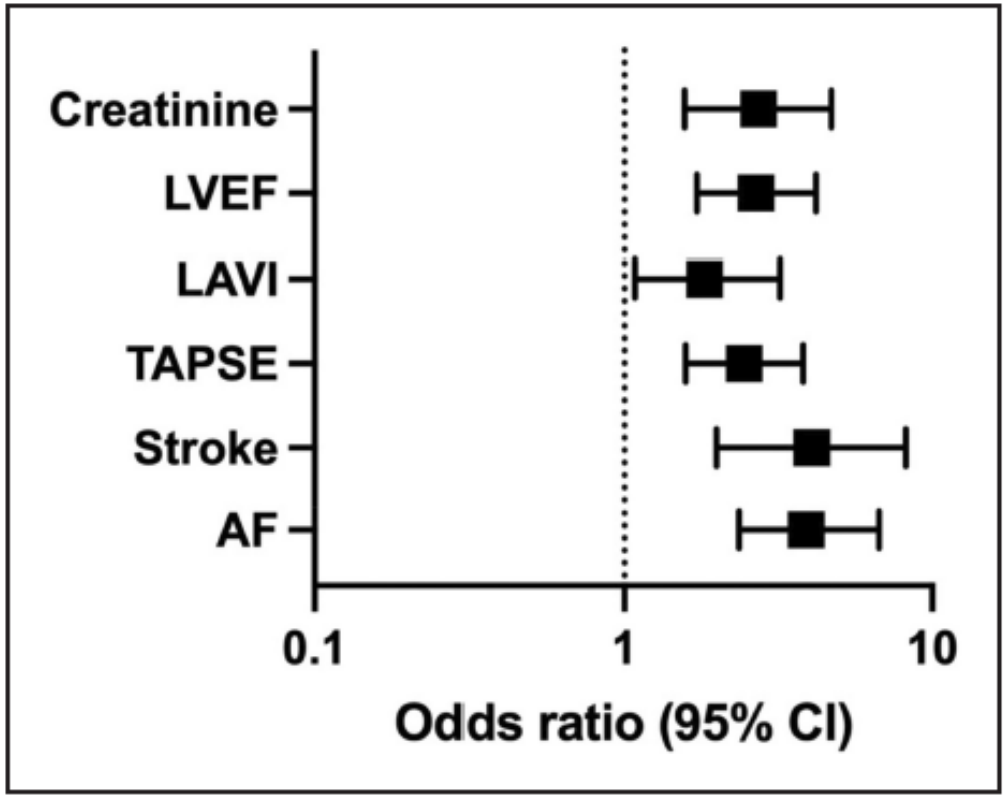
Weighted CLOTS2-AF beta coefficient values

	Covariate	OR	p value	Beta coefficient
C	Creatinine >132	2.724 (1.57-4.70)	<0.001	1.002
L	LVEF <50	2.68 (1.72-4.20)	<0.001	0.987
O	Overload (LAVI >34)	1.82 (1.08-3.20)	0.031	0.597
T	TAPSE <17	2.45 (1.58-3.81)	<0.001	0.896
S	Stroke	4.07 (1.99-8.20)	<0.001	1.403
AF	Atrial fibrillation	3.90 (2.36-6.72)	<0.001	1.361

Odds ratios of component CLOTS-AF covariates



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CLOTS-AF score

CLOTS-AF score		Points (0-12)
C	Creatinine Creatinine >1.5mg/dL	2
L	LV systolic dysfunction LVEF<50%	2
O	Overload LAVI >34ml/m^2	1
T	TAPSE TAPSE<17mm	2
S	Stroke	3
AF	AF rhythm	2

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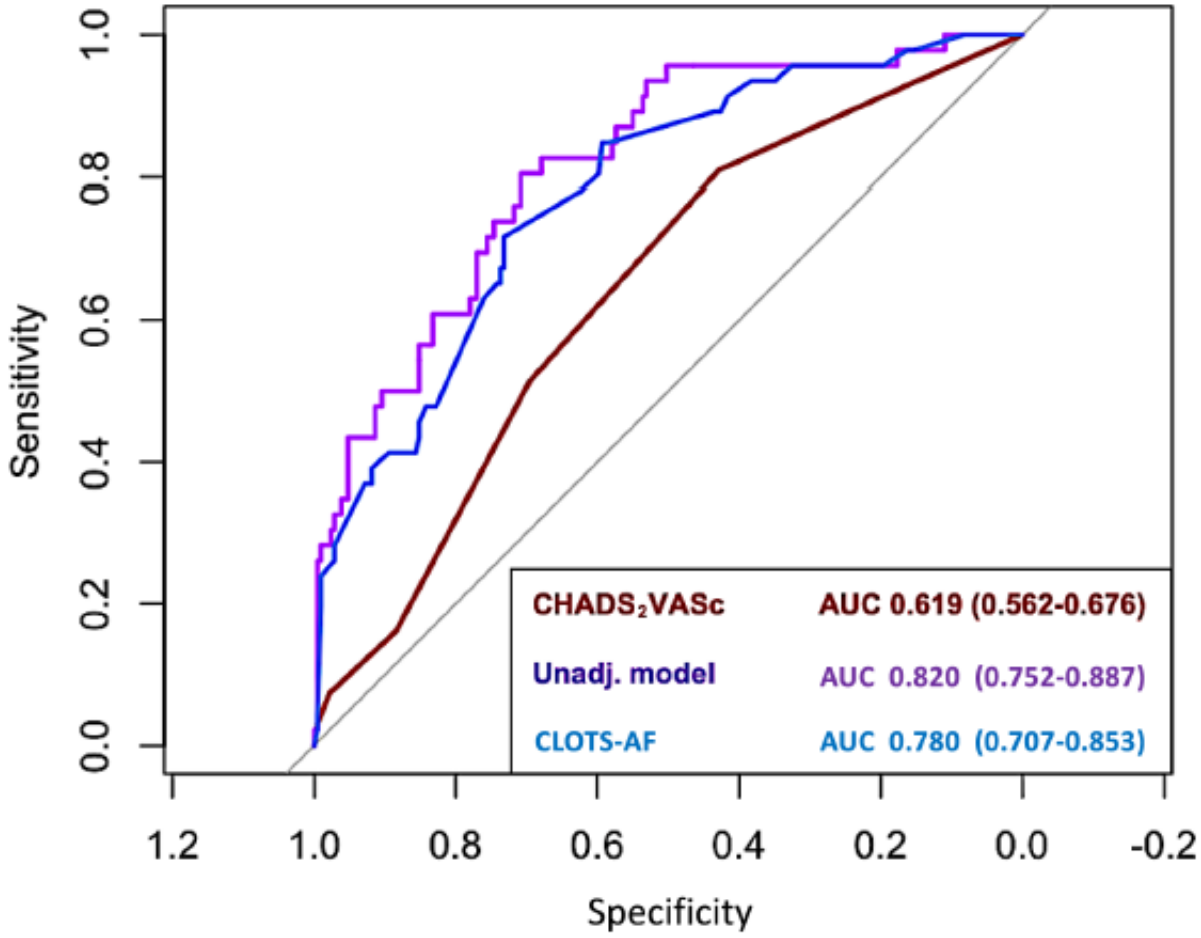
AUC of unadjusted model and CLOTS-AF risk score (blue) compared with CHADS2VASc score (brown)

- On average, each 1-point increment in the CLOTS-AF risk score was associated with a nearly 2-fold increased risk of LAAT (OR, 1.63 [95% CI, 1.47–1.83]; P<0.001).
- A risk score of ≥6 was considered a statistically significant threshold on Youden's index, with a nearly 6-fold increase in LAAT risk (OR, 5.67 [95% CI, 3.62–9.00]; P<0.001)



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Characteristics Among Individuals With LAAT According to Heart Failure Status

- LAAT was present in 119 of 324 (36.7%) patients with heart failure.
- In those with concurrent heart failure, the presence of LAAT was significantly higher among those:
  - inadequately warfarinized compared with DOAC use;
  - in AF;
  - with more advanced cardiac remodeling (lower LV and RV systolic function, increased atrial and ventricular dimensions, and elevated filling parameters),
  - with renal impairment,
  - with a higher $CHAD_2S_2VASc$ score

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Predictors of LAAT Resolution

Characteristics	OR	95% CI	*P* value
Female sex	0.318	0.091–1.111	0.073
Age >65 y	0.824	0.258–2.626	0.743
Rhythm			
AFL	1.490	0.188–2.817	0.321
PsAF	1.300	0.335–5.053	0.704
AF duration	0.998	0.996–1.001	0.159
AF duration >1 y	0.892	0.135–5.913	0.906
Anticoagulant change	0.378	0.115–1.250	0.111
Obesity (BMI >30 kg/m^2)	1.889	0.641–5.569	0.249
Hypertension	1.190	0.333–4.254	0.789
Dyslipidemia	1.163	0.298–4.530	0.828
Creatinine	0.997	0.991–1.004	0.425
Prior MI	0.870	0.234–3.240	0.836
Prior stroke	0.579	0.101–3.305	0.539
LVEF <50%	1.479	0.593–3.687	0.401
LAVI >35 mL/m^2	0.941	0.322–2.746	0.912
Warfarin post TEE	1.731	0.666–4.500	0.260

- In the LAAT cohort, 94 individuals underwent serial TEE imaging. Of those, anticoagulation had not been commenced before TEE in 13.9%, was of inadequate duration or compliance in 30%, or required TEE in the setting of subtherapeutic INR in 56.1%.
- Thrombus had resolved to enable cardioversion in 59 (63%) at a median of 133 days (IQR, 52–289) after index TEE.
- Despite the presence of LAAT at index TEE, anticoagulant adjustment was uncommon (20%) and did not predict thrombus resolution.
- Clinical and echocardiographic parameters and anticoagulant type did not predict thrombus resolution in this population

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Limitations

- The study population is a selected cohort of patients with AF/AFL and inadequate anticoagulation before cardioversion and does not report the true prevalence of LAAT among the general AF/AFL population.
- This was a single-center retrospective analysis of LAAT incidence. External validation would strengthen the predictive power and clarify the application of this risk model to the general AF/AFL population undergoing rhythm control; however, there are no established large-scale databases of this nature to facilitate such an analysis.

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Conclusions

- Clinical and noninvasive echocardiographic parameters predicted LAAT among a large population undergoing TEE before DCR for AF/AFL.
- The novel CLOTS-AF score may enhance LAAT risk prediction and help identify patients at higher risk for LAAT in whom a period of therapeutic anticoagulation is more suitable rather than an expedited TEE-guided cardioversion.

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Clinical perspective

What Is New?

- Noninvasive clinical and echocardiographic parameters can predict left atrial appendage thrombus risk in patients with atrial fibrillation/atrial flutter undergoing transesophageal echocardiography–guided direct cardioversion.
- Despite this, there is a distinct lack of a universal risk stratification schema to guide the need for preprocedural transesophageal echocardiographic imaging.
- The CLOTS-AF risk model is readily applied in the clinical context and outperformed the $CHADS_2VASc$ score with regard to left atrial appendage thrombus risk prediction.

What Are the Clinical Implications?

- A novel risk score incorporating noninvasive clinical and echocardiographic parameters may identify high-risk individuals in whom a period of anticoagulation should be initiated rather than undertaking a strategy of early transesophageal echocardiography–guided cardioversion, with a high likelihood of left atrial appendage thrombus.
- External validation could clarify the broader clinical utility of the proposed risk model in diverse populations and clinical settings.

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