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Original Article

Predictors of Device-Related Thrombus After Left Atrial Appendage Occlusion: TED-F_2 Score

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ABSTRACT

Background: Left atrial appendage (LAA) occlusion (LAAO) is performed to prevent LAA thrombus in patients with atrial fibrillation (AF). The risk of device-related thrombus (DRT) on the atrial side of the LAAO device is approximately 4%. Identifying patients at high risk of DRT would enable closer surveillance and more-aggressive anticoagulation to prevent post-LAAO DRT-related stroke.

RÉSUMÉ

Résumé : La fermeture de l'appendice auriculaire gauche (AAG) sert à prévenir la formation d'un thrombus à l'AAG en présence d'une fibrillation auriculaire (FA). Le risque de formation de thrombus du côté auriculaire du dispositif de fermeture de l'AAG est d'environ 4 %. La capacité de déterminer quels patients présentent un risque élevé de formation de thrombus liée au dispositif permettrait une surveillance

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a lifetime estimated risk of 1:4 to 1:3 individuals. AF is associated with an increased risk of systemic thromboembolic events, including a 5-fold increased risk of ischemic stroke.[1,2] The left atrial (LA) appendage (LAA) is the site of thrombus formation in > 90% of patients with nonvalvular AF who develop an intracardiac thrombus.[3] Oral anticoagulation effectively reduces this risk of cardioembolism and is the standard of care.[4]

LAA occlusion (LAAO) using a percutaneously delivered catheter-mounted device is becoming an increasingly popular and widely used alternative to reduce the risk of systemic thromboembolism in patients with nonvalvular AF who are not suitable for or do not want long-term anticoagulation. A transesophageal echocardiogram (TEE) or cardiac computed tomography angiography (CCTA) is performed 45 days and 1 year after device implantation to assess for effective LAAO. In the absence of a significant peridevice leak (or device-related thrombus [DRT]) at 45-day post-LAAO imaging, anticoagulation routinely is discontinued. LAA imaging often is repeated in cases of clinical systemic cardioembolic events, such as transient ischemic attack and/or cerebrovascular accident (TIA/CVA).[5]

The overall risk of DRT is reported to be 3.7%-4.2%.[6-9] Although most cases of DRT occur within the first year,[8] and especially within the first few months,[10] after device implantation, DRT detected as late as 5-10 years after implantation has been reported.[11,12] The risk of stroke and systemic embolism in patients with DRT has been reported to be as high as 25%.[9] Patients with DRT are at a 3-5 times greater risk of developing stroke, compared to patients without DRT.[9,13,14] On diagnosis of DRT, antithrombotic therapy usually is resumed or intensified, as tolerated by the patient. Current practices regarding continued follow-up LAA imaging for DRT surveillance are not uniform, due to a paucity of literature on risk predictors and the timing of DRT. We aimed to establish a clinical risk-prediction model, to

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Methods: From the LAAO registry at The University of Kansas Medical Center, we identified patients who developed DRT. We chose 3 unmatched controls per DRT case from LAAO recipients without DRT. Predictor variables were obtained from transesophageal echocardiogram reports and/or images, transthoracic echocardiogram reports, and chart review. Implant depth was measured from the limbus of the left atrial ridge to the centre of the atrial aspect of the LAAO device, on a 45° transesophageal echocardiogram view.

Results: We identified 26 patients with DRT (aged 77.7 ± 9.7 years; 34.6% female) and selected 78 unmatched controls without DRT. Univariate predictors of DRT, comprising a novel TED-F_2 score, included history of venous **T**hromboembolism (23.1% vs 5.1%, $P = 0.01$), an LAA **E**mptying velocity ≤ 20 cm/s (45.8% vs 18.9%, $P = 0.01$), an implant **D**epth > 2 cm (34.6% vs 12.8%, $P = 0.02$), and presence of **AF** rhythm at time of device implantation (50.0 % vs 11.5%, $P = 0.0001$). A TED-F_2 score of ≥ 3 was very strongly associated with DRT—odds ratio 12.5 (95% confidence interval, 3.8-41.1, $P < 0.0001$).

Conclusions: We propose a novel risk score to predict development of DRT after LAAO, comprising history of venous **T**hromboembolism, LAA **E**mptying velocity ≤ 20 cm/s, implant **D**epth > 2 cm (1 point each), and an **AF** rhythm at implantation (2 points). A TED-F_2 risk score of ≥ 3 identified patients who are at greatly elevated risk of developing DRT.

Méthodologie : Dans le registre des fermetures de l'AAG du centre médical de l'Université du Kansas (University of Kansas Medical Center), nous avons recensé des patients chez qui un thrombus lié à un dispositif s'était formé. Nous avons choisi au hasard 3 fois plus de patients témoins qui avaient subi une fermeture de l'AAG sans qu'un thrombus lié au dispositif se soit formé. Des variables descriptives ont été obtenues à partir de rapports et/ou d'images d'échocardiogrammes transœsophagiens, de rapports d'échocardiogrammes transthoraciques et d'analyses de dossiers. La profondeur de l'implant était mesurée du limbe de la crête auriculaire gauche au centre du côté auriculaire du dispositif de fermeture de l'AAG, sur une vue échocardiographique transœsophagienne à 45°.

Résultats : Nous avons recensé 26 patients (âgés de 77,7 ± 9,7 ans; 34,6 % de femmes) présentant un thrombus lié au dispositif et nous avons sélectionné 78 témoins non appariés sans thrombus lié au dispositif. Les facteurs prédictifs à variable unique du thrombus lié au dispositif, dont un nouveau score TED-F_2, comprenaient les antécédents de thromboembolie veineuse (23,1 % *vs* 5,1 %, $p = 0,01$), une vitesse de vidange de l'AAG ≤ 20 cm/s (45,8 % *vs* 18,9 %, $p = 0,01$), une profondeur de l'implant > 2 cm (34,6 % *vs* 12,8 %, $p = 0,02$) et présence d'un rythme de fibrillation auriculaire au moment de l'implantation (50,0 % *vs* 11,5 %, $p = 0,0001$). Un score TED-F_2 ≥ 3 était fortement corrélé à la formation d'un thrombus lié au dispositif — rapport de cotes de 12,5 (intervalle de confiance à 95 %, 3,8-41,1; $p < 0,0001$).

Conclusions : Nous proposons un nouveau score de risque pour prédire la formation d'un thrombus lié au dispositif après la fermeture de l'AAG, comprenant des antécédents de thromboembolie veineuse, une vitesse de vidange de l'AAG ≤ 20 cm/s, une profondeur de l'implant > 2 cm (1 point chacun) et un rythme de fibrillation auriculaire à l'implantation (2 points). Un score de risque TED-F_2 ≥ 3 indiquait un risque très élevé de formation de thrombus lié au dispositif.

identify patients at higher risk of DRT who would benefit from receiving closer surveillance or extended antithrombotic treatment to prevent post-LAAO stroke.

Methods

The study proposal was approved by the Institutional Review Board at The University of Kansas Medical Center (KUMC).

Study design, and inclusion and exclusion criteria

This was a retrospective case-control study. Patients for this study were selected from all patients who underwent LAAO, primarily with a Watchman 1st generation or Watchman FLX (Boston Scientific, Marlborough, MA) device, between October 2016 and February 2022 at KUMC, identified from our LAAO registry, comprising 637 patients who had undergone LAAO. Of these 637 LAAO registry patients, 20 developed DRT during follow-up (3.1%) and were included as DRT cases. To increase the statistical power of our analysis, we added another 6 patients to the cases, who had LAAO performed through November 2022 and subsequently developed DRT. For each patient who developed DRT, we included 3 unmatched control patients without DRT, selected at random from the LAAO registry through February 2022.

All LAAO device implantations were performed under TEE guidance. All patients underwent a follow-up TEE (rarely CCTA) at approximately 45 days and 1 year after device implantation. Additional imaging was performed at various timepoints, as indicated for follow-up of peridevice leaks. Our standard protocol was to use an oral anticoagulant (OAC) and aspirin for the first 45 days post—LAAO implantation until the follow-up TEE. If no DRT or significant peridevice leak (≥ 5 mm) was present, the patient was switched to dual-antiplatelet therapy (usually clopidogrel 75 mg daily and aspirin 81 mg daily), and then treatment was reduced to single-antiplatelet therapy (usually aspirin 81 mg daily) alone at 6 months post-LAAO. However, a subset of patients had their first post-LAAO TEE performed at 3 months (eg, those who were undergoing concomitant catheter ablation, those enrolled in clinical LAAO trials, and those determined at the discretion of the operator).

Data collection

After identification of patients from the LAAO registry, we performed a manual electronic medical record chart review to obtain demographic, clinical, laboratory, and

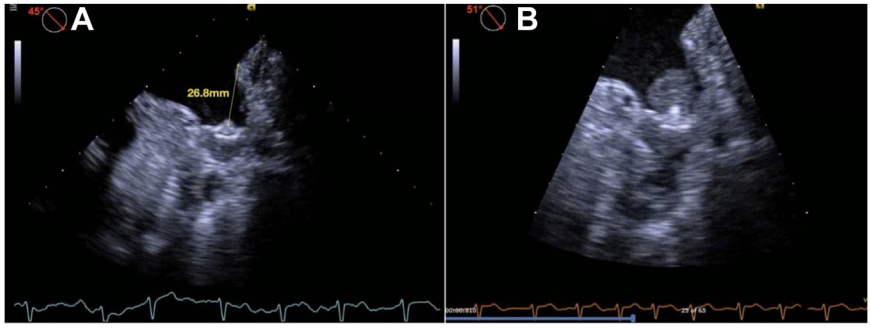

Figure 1. Transesophageal echocardiographic imaging in a patient with a Watchman FLX (Boston Scientific, Marlborough, MA) device implant. (**A**) Implant depth of 26.8 mm, measured as the distance from the limbus of the oblique ridge to the centre of the left atrial aspect of the Watchman device in the 45° view on transesophageal echocardiogram performed at the time of implantation. Such deep implants, especially with depth measurements > 2 cm, should not be accepted as a satisfactory result, and the device should be repositioned more proximally in the left atrial appendage ostium. (**B**) Device-related thrombus, as seen in the 45° view on transesophageal echocardiogram performed at 14 months postimplant. The patient was on single-antiplatelet therapy at the time of diagnosis.

echocardiographic (TEE and transthoracic echocardiogram) variables. Demographics (age, sex, body mass index), comorbidities (hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral arterial disease, history of TIA/CVA, history of venous thromboembolism [VTE], ie, deep vein thrombosis and/or pulmonary embolism, type of AF) and laboratory values (hemoglobin, platelets, estimated glomerular filtration rate) were obtained via patient chart review. The preimplantation transthoracic echocardiogram reports (completed at up to 6 months prior to TEE) were used to record the LA size, LA volume, and left ventricular ejection fraction. Additional echocardiographic variables were recorded by querying the KUMC HERON (Healthcare Enterprise Repository for Ontological Narration) tool.[15,16]

TEE images were reviewed to determine the presence of LA and/or LAA spontaneous echo contrast, the LAA emptying velocity (LAAev), the LAA shape, and LAA ostium and depth measurements, as well as the implant depth and the largest shoulder measurements post-LAAO. The LAAev was obtained in a standard manner, by measuring the pulse Doppler tracing of the LAA. An LAAev of $\leq$ 20 cm/s was categorized as being severely reduced. The implant depth was measured as the distance from the limbus of the LA oblique ridge to the centre of the LA aspect of the LAAO device in the 45° view on TEE (Fig. 1). The LAAO shoulder was measured as the maximum distance of the LAAO device projecting into the left atrium from the level of the LAA ostium in any TEE view. The procedure report and the saved electrocardiogram strip in echo cine loops were the sources of cardiac rhythm data at the time of device implantation. The device size and compression, and the presence vs absence of peridevice leak and DRT, were determined from procedure and postprocedure imaging study reports.

Statistical analysis

Distributions are presented as means $\pm$ standard deviations, or percentages. Univariate and multivariate comparisons between cases and controls were done using logistic regression models, with continuous variables entered as linear predictors or converted to categorical variables as needed. For multivariate analysis, categorical, nonmissing, and noncollinear variables that were most significant in univariate analyses were selected manually and entered into a logistic regression model predicting DRT cases vs controls. Collinearity between predictor variables was suspected based on biological plausibility, and this possibility was assessed statistically using Fisher's exact test, and only the most significant of the collinear variables were added to the multivariable model. The odds ratios from this multivariate model were used to devise a point score for predicting DRT. Statistical analysis was performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

The total study population was 104 patients. The DRT case group included 26 patients who underwent LAAO and developed DRT over the study period. This group included 25 patients who received a Watchman FLX, and 1 who received an Amplatzer Amulet LAA Occluder (Abbott, Santa Clara, CA). Indications for LAAO were severe bleeding for 18 patients, recurrent falls for 4 patients, being enrolled in LAAO trials (including the Amulet implant) for 2 patients, intolerance to oral anticoagulants (dyspnea) for 1 patient, and unspecified unsuitability for anticoagulation treatment for 1 patient. The control group included 78 patients who underwent LAAO and did not develop DRT over the study period. All of the controls had Watchman implants for LAAO, which is reflective of our practice during the registry timeframe used for controls.

DRT group

Among the 26 DRT cases, the diagnosis of DRT was made < 2, 2-4, 4-9, 9-15, and > 15 months in 9, 6, 3, 7, and 1 patient(s), respectively (median: 97.5 days; interquartile range: 47-346 days). For various reasons, TEE diagnosing DRT was performed outside of the per-protocol 45 days and 1 year post-LAAO, including an alternate (3-month) post-LAAO screening protocol (4 patients), other indications for TEE (5 patients), and gastrointestinal bleeding (a 45-day TEE delayed for 1 patient). At the time of DRT diagnosis, 10 patients were on OAC therapy (apixaban [4 patients], rivaroxaban [2

Table 1. Baseline characteristics of study population

Variable	DRT (n = 26)	Control (n = 78)	*P*
Demographics			
Age, y	77.7 ± 9.7	75.3 ± 7.7	0.2
Female, %	34.6	37.2	1
Body mass index, kg/m^2	29.3 ± 6.0	29.7 ± 5.5	0.8
Comorbidities, %			
Hypertension	88.5	92.3	0.7
Diabetes mellitus	15.4	46.2	**0.005**
Congestive heart failure	53.9	36.5	0.2
Coronary artery disease	61.5	52.6	0.5
Peripheral arterial disease	15.4	20.5	0.8
History of cerebrovascular accident and/or transient ischemic attack	38.5	28.2	0.3
History of venous thromboembolism	23.1	5.1	**0.01**
CHA_2DS_2-VASc score	4.5 ± 1.5	4.4 ± 1.7	0.8
Laboratory			
Hemoglobin, g/dL	13.3 ± 2.3	12.4 ± 2.2	0.07
Platelet count, × 1000/L	209 ± 60	206 ± 79	0.9
eGFR, mL/min per 1.73 m^2	64 ± 21	60 ± 24	0.4
Rhythm, %			
Longstanding persistent or permanent atrial fibrillation	53.9	20.5	**0.002**
Rhythm of atrial fibrillation at the time of left atrial appendage occlusion	50.0	11.5	**0.0001**

Values are mean ± standard deviation, or %. Boldface indicates statistical significance.

CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke/TIA, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **c**ategory; DRT, device-related thrombus; eGFR, estimated glomerular filtration rate.

Table 2. Echocardiographic structural and functional characteristics of study population

Variable	DRT (n = 26)	Controls (n = 78)	*P*
LA size, cm	4.76 ± 0.80	4.37 ± 0.87	0.09
LA volume, mL (n = 78)	102.8 ± 44.4	74.4 ± 26.4	**0.001**
LA spontaneous echocontrast, %	26.9	7.7	**0.02**
LAA emptying velocity ≤ 20 cm/s	45.8	18.9	**0.01**
LAA emptying velocity, cm/s	31.4 ± 19.3	37.6 ± 17.7	0.1
LAA shape, %			0.8
Chicken wing	32.0	30.8	
Windsock	36.0	29.5	
LAA measurements, mm			
LAA ostium max	23.6 ± 4.0	21.9 ± 4.0	0.07
LAA ostium min	18.7 ± 3.2	16.9 ± 3.4	**0.01**
LAA ostium area	3.55 ± 1.16	2.98 ± 0.97	**0.02**
LAA depth	27.5 ± 25.4	26.6 ± 6.4	0.5
Left ventricular ejection fraction, %	55.0 ± 12.4	54.9 ± 10.4	1

Values are mean ± standard deviation, or %. Boldface indicates statistical significance.

DRT, device-related thrombus; eGFR, estimated glomerular filtration rate; LA, left atrial; LAA, left atrial appendage; max, maximum; min, minimum.

patients], dabigatran [1 patient] or warfarin [3 patients]), 3 patients were on dual-antiplatelet therapy, and 12 patients were on single-antiplatelet therapy. The 10 patients on OAC therapy at the time of DRT included 9 who were diagnosed on 45-day post-LAAO TEE (prior to planned discontinuation of OAC) and one patient 259 days post-LAAO (with persistent AF and for whom electrical cardioversion and catheter ablation were planned and had OAC resumed periprocedurally). Two patients had not been on OAC therapy since the time prior to LAAO. For the 14 patients who were not on OAC therapy at the time of DRT diagnosis, but who previously were on OAC therapy that had been discontinued at the time of or after LAAO device implantation, the median length of time between discontinuation of OAC therapy and diagnosis of DRT was 303 days (interquartile range: 83-334 days).

Impact of DRT

Two patients with DRT presented with a stroke, and DRT was identified during workup for cause of stroke. Both of these patients were on single-antiplatelet therapy at the time of DRT diagnosis and then were started on apixaban. They were, respectively, 101 days and 233 days from LAAO. One of them had a large—2 × 2 cm—LA thrombus, in addition to a thrombus on the LAAO device, and this patient underwent surgical thrombectomy. The second patient's DRT was noted to have resolved on TEE performed at 2.5 months. The other 24 DRT patients were asymptomatic and were identified on routine post-LAAO surveillance imaging. One patient had a very small DRT and was having frequent falls. Thus, anticoagulation therapy was not resumed, and follow-up care was not available. In all other patients, OAC therapy was continued or resumed (apixaban [13 patients], rivaroxaban [6 patients], warfarin [4 patients]).

Of the 23 patients who had a follow-up imaging evaluation (TEE vs CCTA), the DRT had resolved in 18 (median length of time from DRT diagnosis to resolution, 94 days; interquartile range: 47-346 days). We did not identify any major bleeding or systemic thromboembolic adverse events, including TIA/CVA, during subsequent follow-up in any of our DRT patients. Two patients with DRT that resolved after reinstitution of OAC therapy had a recurrence of DRT after the OAC therapy was discontinued, at 50 and 98 days post-discontinuation, respectively. One of these patients had severe LA enlargement and a deep implant, at > 2 cm. The other patient had permanent AF with severe LA enlargement and a severely reduced LAAev.

Clinical characteristics

Table 1 shows the baseline characteristics of the 2 groups (DRT cases and non-DRT controls). The 2 groups had similar demographic and laboratory characteristics. Among the comorbidities, the prevalence of diabetes mellitus was higher in the control group (15.4% vs 46.2%, $P = 0.005$). On the other hand, more DRT cases had a history of VTE (23.1% vs 5.1%, $P = 0.01$), had longstanding persistent or permanent AF (53.9% vs 20.5%, $P = 0.002$), and were more often in AF rhythm at the time of LAAO device implantation (50.0% vs 11.5%, $P = 0.0001$).

Table 3. Left atrial appendage device characteristics of study population

Variable	DRT (n = 26)	Controls (n = 78)	*P*
Device size, mm	28.5 ± 3.4	27.8 ± 3.6	0.4
Compressed device maximum size, mm	23.8 ± 4.0	22.5 ± 3.2	0.1
Device compression %	16.9 ± 5.6	18.8 ± 7.7	0.3
Any peridevice leak present, %	19.2	29.5	0.4
Implant depth, mm	18.1 ± 6.5	14.3 ± 5.4	**0.005**
Implant depth > 2 cm	34.6	12.8	**0.02**
Shoulder, mm	3.9 ± 2.8	4.3 ± 3.9	0.5

Values are mean ± standard deviation, or %. Boldface indicates statistical significance.

DRT, device-related thrombus.

Echocardiographic characteristics

On comparison of baseline echocardiographic characteristics (Table 2), patients who developed DRT were found to have a significantly higher mean LA volume (102.8 ± 44.4 vs 74.4 ± 26.4 mL, $P = 0.001$), compared to that of the controls. Also, compared to the controls, a significantly higher proportion of DRT patients has LA spontaneous echocontrast (26.9% vs 7.7%, $P = 0.02$) and a severely reduced LAAev (45.8% vs 18.9%, $P = 0.01$). No significant difference was present in LAA shape or depth between the 2 groups. The LAA ostium was significantly larger in patients who developed DRT, compared to the size in the controls, based on the minimum LAA ostium diameter (18.7 ± 3.2 vs 16.9 ± 3.4 mm, $P = 0.01$) and the estimated LAA ostium area (3.55 ± 1.16 vs 2.98 ± 0.97 cm^2, $P = 0.02$).

Device characteristics

Overall device characteristics (Table 3), such as device size, device compression level, presence of shoulder, and presence of peridevice leak, were similar for the case vs control groups. However, patients with DRT had a significantly larger implant depth measurement (18.1 ± 6.5 vs 14.3 ± 5.4 mm, $P = 0.005$), and a larger proportion of these patients had an implant depth > 2 cm (34.6% vs 12.8%, $P = 0.02$), compared to the proportion in the control group.

DRT risk scoring system

We created a multivariable logistic regression model for odds ratios of DRT. We opted to enter only one each of the significant univariate variables that were collinear with each other. We thus chose rhythm at the time of TEE, rather than history of longstanding or permanent AF; and we chose LAAev ≤ 20 cm/s, instead of LA spontaneous echocontrast, increased LA volume, or LAA ostial measurements. We did not enter diabetes mellitus into the multivariate model, as we did not have any putative mechanistic reason to explain the finding of its univariate association with reduced odds of DRT. Analyses with diabetes mellitus included in the multivariable model and in the DRT risk scoring system are provided separately in Supplemental Tables S1-S3. We therefore manually entered the significant variables of history of VTE, severely reduced LAAEv (≤ 20 cm/s), implant depth > 2 cm, and AF rhythm at the time of device implantation in this multivariate model. Based on the relative multivariate odds ratios of developing DRT for each of these variables, we assigned points for each of the 4 variables (Table 4). A DRT risk scoring system was thus created, with each predictor assigned 1 point, except for AF rhythm at the time of implantation, which was allocated 2 points (that is, history of V**T**E, LAA**E**v < 20 cm/s, implant **D**epth > 2 cm (1 point each), and presence of A**F** rhythm at the time of device implantation (2 points) [TED-F_2] score), with a possible range of total score of 0-5. An overall progressive increase occurred, in the odds of developing DRT, with increases in DRT risk score. Compared to a TED-F_2 score of 0, a score of 3, and a score of 4-5, respectively, predicted 13.0 (95% confidence interval [CI] 3.0, 55.9) and 37.1 (95% CI 3.8, 366) times higher odds of developing DRT (Table 5). We categorized patients as having either low risk or high risk for developing DRT, based on a TED-F_2 score of 0-2 and 3-5, respectively. A TED-F_2 score of 3-5, as compared to a score of 0-2, was found to correlate with having 12.5 times higher odds of developing DRT (95% CI 3.8, 41.1, $P < 0.0001$; Table 6).

Discussion

Summary of results

In this study, we identified clinical, echocardiographic, and implant-related predictors of DRT after LAAO device implantation. We found a history of V**T**E, severely reduced LAA**E**v, an implant **D**epth > 2 cm, and an A**F** rhythm at the time of device implantation to be risk predictors for the development of DRT. We developed a risk score (TED-F2), with the above variables assigned 1 point each, except AF rhythm, which was given 2 points. A TED-F_2 score ≥ 3 was associated with 12.5 times higher odds of DRT (Fig. 2). This model provides stronger prediction compared to previously

Table 4. Multivariable model for left atrial appendage occlusion device–related thrombus risk predictors

Variable	Univariate odds ratio	*P*	Multivariate* odds ratio	*P*	TED-F2 score points
History of VTE	5.55	**0.01**	2.48	0.3	1
LAAEv ≤ 20 cm/s	3.67	**0.01**	2.29	0.1	1
Deep implant (> 2 cm)	3.60	**0.02**	2.27	0.2	1
Atrial fibrillation rhythm at time of device implantation	7.67	**0.0001**	4.52	**0.009**	2

Boldface indicates significance.

TED-F_2 score, history of V**T**E, severely reduced LAA**E**v, implant **D**epth > 2 cm (1 point each), and A**F** rhythm at the time of device implantation (2 points); LAAEv, left atrial appendage emptying velocity; VTE, venous thromboembolism.

*Multivariate model area under the ROC curve, 0.75.

Table 5. Odds ratios of developing device-related thrombus (DRT) for different TED-F_2 scores (history of VTE, LAAEv $\leq$ 20 cm/s, implant Depth $>$ 2 cm [1 point each], and presence AF rhythm at the time of device implantation [2 points])*

TED-F_2 score	n	DRT	Control	Odds ratio (95% CI)
0	59	7	52	Reference
1	18	5	13	2.9 (0.8, 10.5)
2	10	2	8	1.9 (0.3, 10.6)
3	11	7	4	13.0 (3.0, 55.9)
4-5	6	5	1	37.1 (3.8, 366)

AF, atrial fibrillation; CI, confidence interval; LAAEv, left atrial appendage emptying velocity; VTE, venous thromboembolism.

*Model area under the ROC curve, 0.76.

published risk predictors and scoring systems. Given the unpredictability of developing DRT, and the potential grave complication of cardioembolic stroke that can occur due to DRT, identifying patients at a higher risk of DRT would be beneficial for patient selection for LAAO, closer DRT surveillance with TEE and/or CCTA after LAAO, and consideration of a preemptive extended antithrombotic regimen.

Clinical implications of DRT

The clinical implications of the development of DRT are not clearly understood. Multiple studies have shown DRT to be associated with a significantly increased risk of TIA/CVA.[8,9,13,17] In contrast, other studies suggest that DRT may not result in an increase in the incidence of stroke or systemic embolism.[7,10,18] The prevalence of outcomes of DRT may be underestimated, as imaging performed for a stroke after LAAO may not detect the DRT, due to complete embolization of the thrombus. Some evidence has indicated an increased incidence of mortality in patients who develop DRT after LAAO,[19] whereas another study reported no increase in mortality incidence in patients with DRT.[13]

The literature regarding treatment response to medical management of DRT is also variable. Some studies have reported a complete resolution of the DRT with continuation or reinitiation of oral anticoagulation therapy.[18,20] However, many patients undergoing LAAO in the real world may not be good candidates for anticoagulation therapy. Given this practical limitation, DRT has been shown to persist in 20%-25% of patients, on follow-up imaging, despite intensification of treatment, as possible for their case.[10,13,19,20] The higher risk of stroke and mortality appears to be worse in patients with residual DRT, compared to that in patients who experience complete resolution.[19]

Table 6. Odds ratios of developing device-related thrombus in low-risk and high-risk categories*

Risk category	TED-F_2 score	Odds ratio (95% CI)
Low	0−2	Reference
High	3−5	12.5 (3.8, 41.1)

TED-F_2 score, history of VTE, LAAEv $\leq$ 20 cm/s, implant Depth $>$ 2 cm (1 point each), and presence of AF rhythm at the time of device implantation (2 points); VTE, venous thromboembolism.

*Model area under the ROC curve, 0.70.

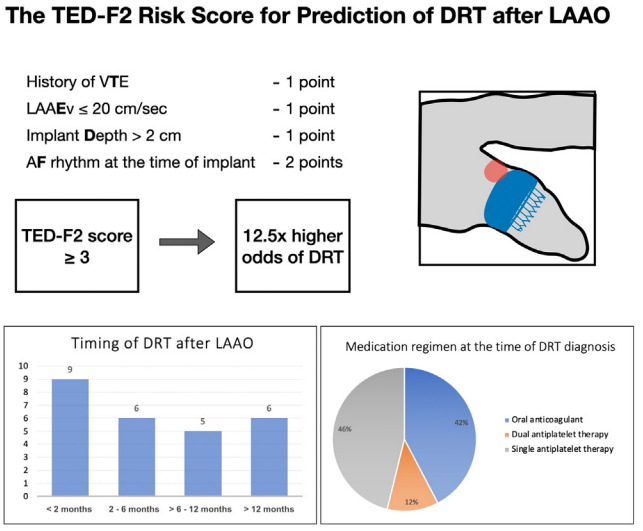

Figure 2. Illustrative summary. AF, atrial fibrillation; DRT, device-related thrombus; LAAO, left atrial appendage occlusion; LAAEv, left atrial appendage emptying velocity; TED-F_2 score, history of VTE, LAAEv $\leq$ 20 cm/s, implant Depth $>$ 2 cm (1 point each), and presence of AF rhythm at the time of device implant (2 points); VTE, venous thromboembolism.

DRT recurrence

Another consideration is follow-up imaging for surveillance of recurrent DRT after resolution of first DRT. Two patients in our study had recurrence of DRT after documented resolution of first DRT. Other isolated case reports have been made of DRT recurrence after documented resolution.[21,22] In a study that analyzed patients undergoing LAAO at 8 centres in Europe and Canada, from 2014 through 2018, who developed and then had complete resolution of DRT, recurrence of DRT occurred in 35% of the patients over a median follow-up of 15 months post−initial thrombus resolution.[20] When categorized by medication regimen after resolution of first DRT, 75% of the patients who were on no antiplatelet or anticoagulant therapy, 38% of the patients on single- or dual-antiplatelet therapy, and none of the patients on anticoagulant therapy developed DRT recurrence. The authors reported that the recurrent DRTs predominantly were clinically silent, possibly highlighting the importance of surveillance imaging.

Risk prediction of DRT

The risk predictors included in our TED-F_2 score have been identified as predictors of a higher risk of DRT in prior studies as well, validating our findings. A large retrospective multicentre study by Simard et al., of 237 patients with DRT and 474 patients without DRT, found 5 DRT risk predictors, as follows: hypercoagulability disorder (4 points); periprocedural iatrogenic pericardial effusion (4 points); renal insufficiency (1 point); implantation depth from LA ridge $>$ 10 mm (1 point); and nonparoxysmal AF (1 point). A total score of $\geq$ 2 was considered high risk and was associated with a 2.1-fold increased risk of DRT.[13] None of our patients developed a periprocedural pericardial effusion, so we are unable to assess it in our analysis, and an approach may be to consider such patients as being at elevated risk of DRT in the short term,

regardless of the TED-F_2 score. We did not find an association of DRT with renal insufficiency. However, history of VTE and AF rhythm at the time of implantation in our study may be interchangeable with presence of a hypercoagulability disorder and nonparoxysmal AF, respectively, in this prior study. Our methodology for measuring the LAA device implantation depth was different, with the measurement made to the centre, as opposed to the edge, of the LA aspect of the device, as we found this location to be more reliable for making the measurement, due to the ridge overhanging the LAAO device in some patients. Regardless of these caveats, utilizing the Simard scoring system to categorize our patients into 2 groups (high-risk and low-risk), or multiple groups by exact Simard score, we obtained c-statistics of 0.58 and 0.66, respectively, for predicting DRT in our dataset. In contrast, with a TED-F_2 score to categorize patients into high-risk and low-risk groups, or multiple groups, based on exact TED-F_2 score, we obtained c-statistics of 0.70 and 0.77, respectively, although this better categorization is reported from the derivation dataset rather than an independent dataset.

Another small study by Pracon et al. on 99 patients undergoing LAAO with either an Amulet or Watchman device, identified DRT in 7 patients and found the risk factors to be history of thromboembolism, lower left ventricular ejection fraction, deep device implantation, and larger devices.[23] Prior VTE and deeper device implantation were common risk factors identified; however, we did not find an association with lower left ventricular ejection fraction or LAAO device size. A small prospective study of 119 patients undergoing Watchman implantation, 2006-2014, found that younger age, chronic AF, a larger device size, a higher Congestive heart failure, Hypertension, Age, Diabetes, Stroke/transient ischemic attack ($CHADS_2$) score, a higher grade of spontaneous echocontrast, and off-protocol anticoagulation and/or antiplatelet therapy were associated with an increased risk of DRT, which occurred in 4 patients. All 4 patients had deviated from the recommended anticoagulant and/or antiplatelet protocol.[18] Again, the predictors of having a severely reduced LAAev, and an AF rhythm at the time of implantation, in our study may be analogous to higher-grade spontaneous echocontrast and chronic AF, respectively, in this prior study. Our study did not find an association of age and device size with risk of developing DRT. Only 2 of the patients in our DRT group did not receive any OAC therapy postimplantation. Multiple other studies also have reported no association of DRT formation with the antiplatelet and/or anticoagulant regimen after LAAO.[10,13,23]

We included AF rhythm at the time of LAAO in the TED-F_2 scoring system, as it was more significant than longstanding persistent and/or permanent AF. No direct causal mechanism has been identified for rhythm at the time of LAAO causing DRT at a future time. Presence of an AF rhythm at the time of LAAO is probably a marker of other correlated risk factors, such as presence of permanent AF, high likelihood of AF during subsequent follow-up, severe left atrial enlargement, poor left atrial mechanical function, diastolic heart failure, etc. Whether rhythm control could reduce DRT is unclear and should be explored in future studies.

An interesting observation in our study is that diabetes mellitus was present significantly less frequently in those who developed DRT, despite diabetes mellitus being generally understood to increase thrombogenesis. This finding is in line with a similar finding from the prior large multicentre study by Simard et al,[13] who thought this result was spurious.But given that our analysis found the same association, this association warrants further exploration to see if it can be confirmed, and if so, to understand its mechanism. Due to the remote biological plausibility of diabetes mellitus preventing DRT, we did not include diabetes mellitus in the TED-F_2 scoring system. However, we have included the multivariable analysis, including diabetes mellitus and derivation of the $TEDF_2D_{-2}$ score (TED-F_2 score additionally with 2 negative points for diabetes mellitus), in Supplemental Tables S1-S3.

A concerning finding is that 10 of the 26 DRTs we found (42%) occurred despite the patient being on OAC therapy, including 7 who were on direct OACs. With the caveat of having used small numbers of cases, we did an exploratory analysis to identify any high-risk predictors of developing DRT despite receiving OAC therapy. The patients who had DRT that developed on OAC therapy (often early on, ~45 days postimplant TEE in 90%) were not different statistically from the other DRT patients who were not on OAC therapy, in demographics, and clinical and echocardiographic characteristics, with the exception that more patents with DRT and on OAC therapy had diabetes mellitus (40% vs 0%, $P = 0.01$), although this finding more likely is a false positive owing to performance of multiple testing (see Supplemental Table S4). Apparently, patients who are at elevated risk of DRT may not be protected completely by standard OAC therapy, especially direct OAC therapy. Whether use of warfarin, as opposed to direct oral anticoagulants, is a more effective treatment strategy post-LAAO, as it is post—mechanical heart valve implantation, remains speculative.[24,25] The existing literature on using direct OACs for post-LAAO anticoagulation protocols suggests that this strategy is effective, similar to warfarin use, although trials with direct head-to-head comparisons are not available.[26]

Study limitations

This is a single-centre study, with a small study size and a retrospective study design. We had limited follow-up for the patients, owing to which asymptomatic or delayed DRT may have been missed. Reflective of the small sample size, in the multivariable model, 3 of the 4 components of the TED-F_2 score were statistically nonsignificant. Further, we did not have a validation dataset, and use of the TED-F_2 score needs to be validated in an independent dataset, prior to its widespread adoption in clinical practice.

Conclusion

Using a case-control design, we identified risk factors for developing post-LAAO DRT, and created a novel, strongly predictive DRT risk scoring system—that is, the TED-F_2 score, comprising history of V**T**E, severely reduced LAA**E**v ($\leq$ 20 cm/s), implant **D**epth $>$ 2 cm (1 point each), and presence of A**F** rhythm at the time of device implantation (2 points). Utilizing the TED-F_2 scoring system, especially when the score is $\geq$ 3, may help identify the patients who are at high risk for development of DRT after LAAO, which may guide the development of individualized antithrombotic and follow-up imaging surveillance plans for each patient. This

approach, consequently, could improve patient outcomes by preventing post-LAAO systemic embolism and stroke.

Clinical Perspectives

- Predicting which patients are at high risk of device-related thrombus after LAAO would enable closer surveillance and individualized anticoagulation strategies.
- We propose the novel TED-F_2 risk score for development of DRT after LAAO (history of V**T**E, LAA**E**v $\leq$ 20 cm/s, implant **D**epth $>$ 2 cm [1 point each], and A**F** rhythm at the time of implantation [2 points]). A TED-F_2 score of 3-5, as compared to score of 0-2, was found to correlate with 12.5 times higher odds of developing DRT.
- The TED-F_2 score needs to be validated in an independent dataset prior to widespread adoption of its use in clinical practice.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective study using de-identified data; therefore, the IRB did not require consent from the patients.

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Disclosures

Dr. Madhu Reddy is on the Advisory board for Boston Scientific Corporation.

References

1. Son MK, Lim NK, Kim HW, Park HY. Risk of ischemic stroke after atrial fibrillation diagnosis: a national sample cohort. PLoS One 2017;12:e0179687.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. Circulation 2023;147:e93-621.
3. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-9.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
5. Saw J, Holmes DR, Cavalcante JL, et al. SCAI/HRS expert consensus statement on transcatheter left atrial appendage closure. Heart Rhythm 2023;20:e1-16.
6. Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. CatheterCardiovasc Interv 2017;90:E111-21.
7. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure. Circulation 2011;123:417-24.
8. Alkhouli M, Busu T, Shah K, et al. Incidence and clinical impact of device-related thrombus following percutaneous left atrial appendage occlusion. JACC Clin Electrophys 2018;4:1629-37.
9. Dukkipati SR, Kar S, Holmes DR, et al. Device-related thrombus after left atrial appendage closure. Circulation 2018;138:874-85.
10. Sedaghat A, Nickenig G, Schrickel JW, et al. Incidence, predictors and outcomes of device-related thrombus after left atrial appendage closure with the WATCHMAN device—insights from the EWOLUTION real world registry. Catheter Cardiovasc Interv 2021;97:E1019-24.
11. Nasser R, Meyten N, Vermeersch P, Prihadi EA. When the solution becomes the problem: left atrial appendage occlusion device-related thrombus after 5 years. Eur Heart J 2021;43:1015.
12. Shamim S, Magalski A, Chhatriwalla AK, et al. Transesophageal echocardiographic diagnosis of a WATCHMAN left atrial appendage closure device thrombus 10 years following implantation. Echocardiography 2017;34:128-30.
13. Simard T, Jung RG, Lehenbauer K, et al. Predictors of device-related thrombus following percutaneous left atrial appendage occlusion. J Am Coll Cardiol 2021;78:297-313.
14. Zhang S, Xiong S-h, Guan Y-g, et al. An updated meta-analysis of device related thrombus following left atrial appendage closure in patients with atrial fibrillation. Systematic review. Front Cardiovasc Med 2022;9:1088782.
15. Waitman LR, Warren JJ, Manos EL, Connolly DW. Expressing observations from electronic medical record flowsheets in an i2b2 based clinical data repository to support research and quality improvement. AMIA Annu Symp Proc 2011;2011:1454-63.
16. Murphy SN, Weber G, Mendis M, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). J Am Med Inform Assoc 2010;17:124-30.
17. Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. J Am Coll Cardiol 2018;71:1528-36.
18. Kubo S, Mizutani Y, Meemook K, et al. Incidence, characteristics, and clinical course of device-related thrombus after Watchman left atrial appendage occlusion device implantation in atrial fibrillation patients. JACC Clin Electrophys 2017;3:1380-6.

19. Sedaghat A, Vij V, Al-Kassou B, et al. Device-related thrombus after left atrial appendage closure: data on thrombus characteristics, treatment strategies, and clinical outcomes from the EUROC-DRT-Registry. Circ Cardiovasc Interv 2021;14:e010195.

20. Asmarats L, Cruz-González I, Nombela-Franco L, et al. Recurrence of device-related thrombus after percutaneous left atrial appendage closure. Circulation 2019;140:1441-3.

21. Nand N, Diab M, Jain D, Shamaki GR, Corteville D. Abstract 14098: early recurrence following resolution of a Watchman device related thrombus. Circulation 2022;146(Suppl_1):A14098.

22. Martinez OC, Bhargav R, Mainigi SK. Recurrent device-related thrombus after Watchman implant. J Am Coll Cardiol 2023;81(8_Suppl):3243.

23. Pracon R, Bangalore S, Dzielinska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. Circ Cardiovasc Interv 2018;11:e005997.

24. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206-14.

25. Wang TY, Svensson LG, Wen J, et al. Apixaban or warfarin in patients with an On-X mechanical aortic valve. NEJM Evid 2023;2:EVIDoa2300067.

26. Tan BE, Wong PY, Lee JZ, et al. Direct oral anticoagulant versus warfarin after left atrial appendage closure with WATCHMAN: updated systematic review and meta-analysis. Curr Probl Cardiol 2022;47:101335.

Supplementary Material

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