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Predictors of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion

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ORIGINAL INVESTIGATIONS

Predictors of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion

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ABSTRACT

BACKGROUND Device-related thrombus (DRT) has been considered an Achilles' heel of left atrial appendage occlusion (LAAO). However, data on DRT prediction remain limited.

OBJECTIVES This study constructed a DRT registry via a multicenter collaboration aimed to assess outcomes and predictors of DRT.

METHODS Thirty-seven international centers contributed LAAO cases with and without DRT (device-matched and temporally related to the DRT cases). This study described the management patterns and mid-term outcomes of DRT and assessed patient and procedural predictors of DRT.

RESULTS A total of 711 patients (237 with and 474 without DRT) were included. Follow-up duration was similar in the DRT and no-DRT groups, median 1.8 years (interquartile range: 0.9-3.0 years) versus 1.6 years (interquartile range: 1.0-2.9 years), respectively ($P = 0.76$). DRTs were detected between days 0 to 45, 45 to 180, 180 to 365, and >365 in 24.9%, 38.8%, 16.0%, and 20.3% of patients. DRT presence was associated with a higher risk of the composite endpoint of death, ischemic stroke, or systemic embolization (HR: 2.37; 95% CI, 1.58-3.56; $P < 0.001$) driven by ischemic stroke (HR: 3.49; 95% CI: 1.35-9.00; $P = 0.01$). At last known follow-up, 25.3% of patients had DRT. Discharge medications after LAAO did not have an impact on DRT. Multivariable analysis identified 5 DRT risk factors: hypercoagulability disorder (odds ratio [OR]: 17.50; 95% CI: 3.39-90.45), pericardial effusion (OR: 13.45; 95% CI: 1.46-123.52), renal insufficiency (OR: 4.02; 95% CI: 1.22-13.25), implantation depth >10 mm from the pulmonary vein limbus (OR: 2.41; 95% CI: 1.57-3.69), and non-paroxysmal atrial fibrillation (OR: 1.90; 95% CI: 1.22-2.97). Following conversion to risk factor points, patients with ≥2 risk points for DRT had a 2.1-fold increased risk of DRT compared with those without any risk factors.

CONCLUSIONS DRT after LAAO is associated with ischemic events. Patient- and procedure-specific factors are associated with the risk of DRT and may aid in risk stratification of patients referred for LAAO.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CT = computed tomography

DAPT = dual antiplatelet therapy

DRT = device-related thrombus

IQR = interquartile range

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

MACE = major adverse cardiac event

OAC = oral anticoagulation

OR = odds ratio

PDL = peridevice leak

SAPT = single antiplatelet therapy

TEE = transesophageal echocardiography

Left atrial appendage occlusion (LAAO) offers an alternative to anticoagulation for prevention of stroke in selected patients with atrial fibrillation (AF) (1,2). Growing operator experience coupled with technical improvements have reduced procedural complications and accelerated continued growth in LAAO (3,4). However, certain challenges with LAAO remain (5–7). Among those, device-related thrombus (DRT) is considered an important issue that may affect the success of the LAAO field at large (2,6,8). Current published reports suggests that DRT occurs in 3% to 4% of patients post-LAAO, and that DRT is associated with a significantly elevated risk of ischemic events (5,6,9). The management of DRT is challenged by lack of reproducible diagnostic criteria, optimal detection protocols, and management strategies, all of which remain to be discerned (5,7). In addition, identifying risk factors for DRT formation has remained elusive with discrepant patient, anatomic, technical, and pharmacologic factors described in several small studies (5,6,9,10). We sought to identify independent predictors of DRT in an international, multicenter dedicated registry to facilitate risk stratification and practice optimization to mitigate this complication.

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METHODS

STUDY COHORT. Participating centers provided data on all DRT cases identified at their center, with 2 corresponding control cases for each DRT case. Control cases were collected by identifying 2 non-DRT cases implanted with the same device type that were temporally adjacent to the respective DRT cases to mitigate selection bias as possible. In this way, an anonymized, retrospective, patient-level, international data set was collated from all centers—the LAAO-DRT registry. The overall time period of the reported cases and total number of LAAO procedures performed in that interval were also recorded.

STUDY DATA AND OUTCOMES. Baseline characteristics, medications, and investigations prior to LAAO

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were collected. LAA anatomy, LAAO implant details, and the DRT diagnosis were documented as detected by computed tomography (CT) or transesophageal echocardiography (TEE). Implantation depth was measured from the pulmonary vein limbus to the atrial aspect of the device to standardize measurement across varying anatomies and device types (10). The presence of any peridevice leak (PDL) was documented, quantified, and classified according to <3 mm, 3 to 5 mm, >5 mm in size. Device migration was defined as any change in device position (rotation or translation) noted during any follow-up imaging assessment as compared to the procedural implant position. High risk AF included the presence of hypertrophic cardiomyopathy, ≥moderate mitral stenosis, or prior mitral valve repair or replacement. Hypercoagulability disorders included any formally diagnosed (pre- or post-procedure) arterial or venous thromboembolic disorders including prothrombin gene mutation, antiphospholipid antibody syndrome, protein C/S deficiency, factor V Leiden, thrombocytosis, factor VIII elevation, or active malignancy. Post-LAAO medication regimens were classified as one of the following: none, single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), oral anticoagulation (OAC), SAPT plus OAC, OAC plus heparin (unfractionated or low molecular weight heparin). Medication regimens were documented at discharge, prior to and immediately following DRT diagnosis, and at last known follow-up. Clinical follow-up was recorded up until the last known follow-up available. The study outcomes included: 1) DRT management patterns; 2) mid-term outcomes of DRT recorded as major adverse cardiovascular events (MACEs) (a composite of ischemic stroke, systemic embolism, and death), any bleeding (TIMI [Thrombolysis In Myocardial Infarction] major or minor), and intracranial hemorrhage; and 3) predictors of DRT. Additional analyses including center volume outcomes and sensitivity analyses for predictors of early versus late DRT and MACE.

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or median (interquartile range [IQR]) (ie, duration of follow-up) and categorical variables were reported as proportions. Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test when applicable. Chi-square or Fisher exact test was used to compare categorical variables. The primary efficacy endpoint of interest was MACE. The primary safety endpoint of interest was a composite of bleeding defined by the TIMI criteria or intracerebral hemorrhage. Overall incidence of MACE, bleeding composite, and its individual components were estimated using the Kaplan-Meier method with corresponding HRs and 2-sided 95% CIs generated by Cox proportional hazards model. Univariate logistic regression was similarly performed for baseline and procedural characteristics that differed between the DRT and control groups. Those with a predetermined $P < 0.20$ in the univariate logistic regression were included in a subsequent multivariable logistic regression analysis and presented as odds ratios (ORs) and 95% CIs. These ratios were then converted to integer values enabling creation of a clinical DRT risk score (11). All statistical analyses were done using SAS version 9.4 (SAS Inc). Figures were created using GraphPad Prism version 8 (GraphPad Software). A value of $P < 0.05$ was considered statistically significant. The Mayo Clinic Institutional Review Board approved the study (#20-002274) with local ethical approval obtained at each of the participating centers.

RESULTS

A total of 37 centers provided data on 711 patients including 474 device-matched control cases and 237 DRT cases for analysis (**Table 1**). In 24 centers for which center volumes were available, DRT occurred in 2.8% of LAAOs performed with no significant association noted between center volume and DRT rates (Supplemental Figure 1). The cohorts were of similar age and sex distribution. The DRT cohort was noted to have a higher proportion of hypertension, congestive heart failure, prior stroke, prior venothromboembolic disorder, hypercoagulability disorders, and high-risk and nonparoxysmal AF. The DRT cohort had a marginally higher CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Age 65-74 years, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Sex female) score (4.6 ± 1.6 vs 4.3 ± 1.5; $P = 0.04$), with no difference in HASBLED score (3.3 ± 1.2 vs 3.3 ± 1.1; $P = 0.86$). LAA morphologies did not differ between either cohort (**Figure 1A**), whereas LAA diameters were slightly larger in the DRT cohort (22.3 ± 5.9 mm vs 21.4 ± 5.6; $P = 0.04$) albeit with similar proportions of LAA diameters >24 mm (34.2% vs 28.2%; $P = 0.19$) (**Table 2**).

PROCEDURAL CHARACTERISTICS AND DEVICE OUTCOMES. In the overall cohort, 74.1% of patients received a Watchman (first-generation 67.2% or FLX 6.9%), and 79.9% were guided by TEE (**Figure 1B, Table 2**). There were no differences between the DRT and control cohorts with respect to device type or

TABLE 1 Demographics

	DRT (n = 237)	Control (n = 474)	*P* Value
Age, y	75.6 ± 8.2	75 ± 8.1	0.25
Sex	146 (61.6)	303 (63.9)	0.52
BMI, kg/m^2	28.8 ± 5.5	28.6 ± 6.1	0.37
Hypertension	212 (89.5)	396 (83.5)	0.03
Dyslipidemia	136 (57.4)	277 (58.4)	0.79
Diabetes mellitus	60 (25.3)	150 (31.6)	0.08
Smoking	13 (5.5)	32 (6.8)	0.51
CHF	100 (42.2)	162 (34.2)	0.04
NYHA functional class	(n = 194)	(n = 377)	0.21
I	92 (38.8)	194 (40.9)	
II	56 (23.6)	91 (19.2)	
III	23 (9.7)	32 (6.8)	
CAD	83 (35.0)	195 (41.1)	0.11
Prior MI	39 (16.5)	89 (18.8)	0.45
Prior PCI	46 (19.4)	107 (22.6)	0.35
Prior CABG	24 (10.1)	58 (12.2)	0.42
Prior CVA	89 (37.6)	145 (30.6)	0.06
Prior ICH	42 (17.7)	72 (15.2)	0.37
Prior VTE	18 (7.6)	24 (5.1)	0.18
Carotid stenosis	18 (7.6)	33 (7.0)	0.76
Peripheral arterial disease	38 (16.0)	62 (13.1)	0.29
Autoimmune disorder	8 (3.4)	11 (2.3)	0.41
Hypercoagulability disorder	11 (4.6)	4 (0.8)	0.0009
Prior bleed	148 (62.4)	303 (63.9)	0.78
TIMI major	48 (20.3)	109 (23.0)	0.41
TIMI minor	82 (34.6)	168 (35.4)	0.82
Prior transfusion	45 (19.0)	95 (20.0)	0.74
Atrial fibrillation/flutter			
Non-paroxysmal	164 (69.2)	252 (53.2)	0.0001
High-risk AF	9 (3.8)	5 (1.1)	0.01
CHA_2DS_2-VASc score	4.6 ± 1.6	4.3 ± 1.5	0.04
>3	172 (72.6)	322 (67.9)	0.21
HASBLED score	3.3 ± 1.2	3.3 ± 1.1	0.86
Pre-LAAO medications			
ASA	77 (32.5)	169 (35.7)	0.33
$P2Y_{12}$	21 (8.9)	51 (10.8)	0.43
Clopidogrel	21 (8.9)	46 (9.7)	
Ticagrelor	0 (0.0)	4 (0.8)	
Prasugrel	0 (0.0)	1 (0.2)	
DOAC	64 (27.0)	150 (31.6)	0.2
Dabigatran	8 (3.4)	11 (2.3)	
Rivaroxaban	18 (7.6)	46 (9.7)	
Apixaban	37 (15.6)	90 (19.0)	
Edoxaban	1 (0.4)	3 (0.6)	
Warfarin	59 (24.9)	91 (19.2)	0.08
IV heparin	1 (0.4)	2 (0.4)	0.99
SQ low-molecular weight heparin	23 (9.7)	22 (4.6)	0.01

Continued on the next page

size implanted (Supplemental Table 1). Device compression was similar between the DRT and control cohorts in both the Watchman (21.0 ± 0.2% vs 19.8 ± 0.2%; $P = 0.36$) and Amplatzer (Abbott) (2.1 ± 0.2% vs 7.5 ± 0.2%; $P = 0.29$) device subgroups. Contrast volume and number of recaptures were similar. DRT cases were found to have deeper device implantations (12.0 ± 8.4 mm vs 8.2 ± 6.5 mm; $P < 0.001$) with a greater proportion of DRT cases (44.3% vs 29.1%; $P < 0.001$) considered to have a deep implant (>10 mm below the pulmonary ridge) (10) (Table 2). Procedural complications were assessed hierarchically and occurred more frequently in the DRT cohort (6.3% vs 2.1%; $P = 0.004$), driven by a higher rate of iatrogenic pericardial effusions (3.4% vs 0.6%; $P = 0.01$) (Table 2). Discharge medical regimens were similar aside from more frequent discharges without antiplatelet or antithrombotic agents in patients experiencing pericardial effusions (0.9% vs 9.1%; $P = 0.007$). Renal function did not affect discharge medication regimens. In follow-up, device migration occurred more commonly in the DRT cohort (2.7% vs 0.0%; $P = 0.002$). PDL was more commonly diagnosed in follow-up (28.0%) than at the time of implantation (6.7%), with PDL being noted more often in the DRT cohort (34.6% vs 26.1%; $P = 0.005$). Moreover, patients with DRT were found to have marginally larger PDL sizes (1.8 vs 1.2 mm; $P = 0.003$) with a greater proportion having ≥1 distinct leak identified (34.2% vs 24.9%; $P = 0.01$) (Table 3).

DIAGNOSIS AND MANAGEMENT OF DRT. DRT diagnosis was made by TEE (200 cases, 84.4%) and CT (33 cases, 13.9%) with TEE plus CT (4 cases, 1.7%) contributing a relatively small amount. Of the 237 DRT cases, 131 (55.3%) were on the disk, 30 (12.7%) were on the screw, 20 (8.4%) were adjacent to the LAAO device, 11 (4.6%) were found elsewhere, 2 (0.8%) on both the screw and the disk, 2 (0.8%) were on the disk and adjacent to LAAO, and 41 (17.3%) were not specified (Supplemental Table 2). The timing of DRT diagnosis varied considerably with 24.9% at <45 days, 38.8% at 45 to 180 days, 16.0% at 180 to 365 days, and 20.3% at >365 days (Figure 2A). Within those time periods, patients with DRT underwent more imaging assessments and experienced greater MACE rates in their respective follow-up intervals, particularly at later time points (>180 days) (Figures 2B and 2C). Medical therapy regimens on discharge following LAAO did not differ between the control and DRT cohorts. At the time of DRT diagnosis, most patients were being managed with either SAPT (36.3%) or DAPT (26.2%). Immediately following DRT diagnosis, there was an increase in anticoagulant use with concomitant decrease in SAPT/DAPT usage. At last known follow-up, 25.3% of patients had

continued presence of DRT, with DRT resolution not portending improved rates of MACE, albeit with limited events. Moreover, patients with a diagnosis of DRT remained on antithrombotic agents at greater rates with more patients being on OAC (19.0% vs 4.2%; $P < 0.001$) or SAPT plus OAC (15.6% vs 2.7%; $P < 0.001$) (**Figure 3B,** Supplemental Figure 2, Supplemental Table 3).

MID-TERM CLINICAL OUTCOMES. Clinical follow-up to last known medical contact demonstrated similar follow-up in both the control and DRT cohorts (median: 1.6 years [IQR: 1.0-2.9 years] vs 1.8 years [IQR: 0.9-3.0 years]; $P = 0.76$). MACEs occurred at greater rates in the DRT cohort (29.5% vs 14.4%, HR: 2.37; 95% CI: 1.58-3.56; $P < 0.001$), driven by increased rates of ischemic stroke (16.9% vs 3.6%; HR: 3.49; 95% CI: 1.35-9.00; $P = 0.01$), with no differences in all-cause mortality or systemic embolism (**Figure 4**). Similarly, both cohorts had comparable rates of bleeding and intracranial hemorrhage during follow-up (**Figure 5**). Among patients who suffered from DRT and stroke, more were diagnosed with DRT prior to the occurrence of stroke (59.0% vs 41.0%) (**Figure 6**). Multivariable analysis assessing for predictors of MACEs following LAAO supported an association of renal insufficiency, prior transfusion, and the presence of DRT with increased risk of MACEs (Supplemental Figure 3).

TABLE 1 Continued

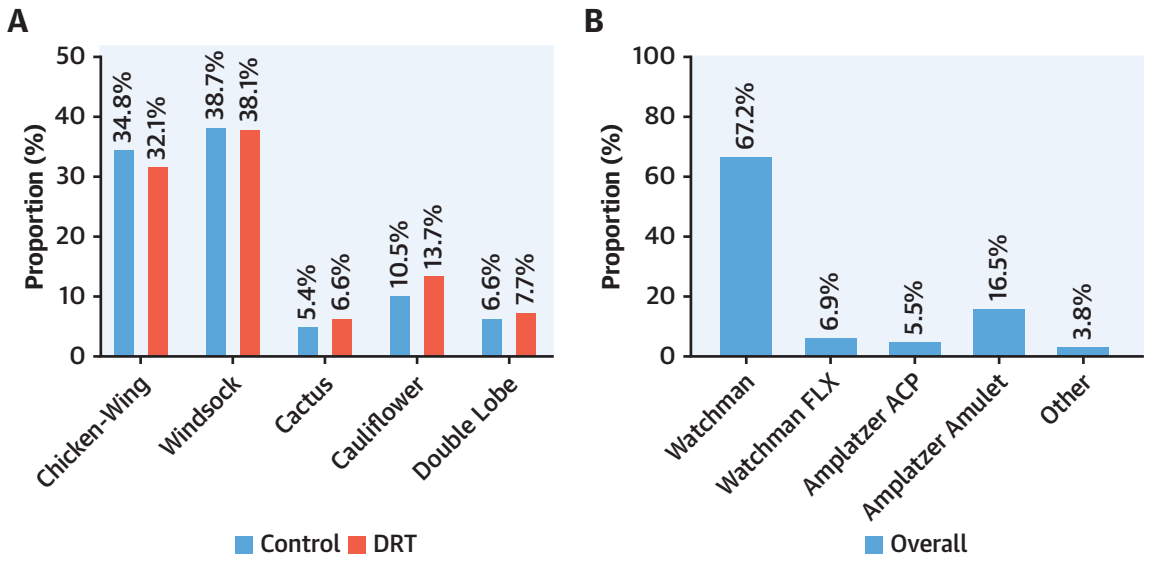
	DRT (n = 237)	Control (n = 474)	*P* Value
Pre-LAAO investigations			
GFR, mL/min (n = 642)	(n = 213)	(n = 429)	0.01
>60	105 (49.3)	259 (60.4)	
30-60	95 (44.6)	139 (32.4)	
<30	13 (6.1)	31 (7.2)	
Hb, g/dL	13.1 ± 2.2	12.9 ± 2.0	0.16
Creatinine, mg/dL	1.3 ± 0.7	1.3 ± 1.1	0.14
LVEF, % (n = 622)	(n = 209)	(n = 413)	0.26
>50	156 (74.6)	328 (79.4)	
35-50	40 (19.1)	58 (14.0)	
<35	13 (6.2)	27 (6.5)	
Mitral stenosis (≥ moderate)	2 (0.8)	1 (0.2)	0.22
Mitral regurgitation (≥ moderate)	49 (20.7)	90 (19.0)	0.59
Aortic stenosis (≥ moderate)	5 (2.1)	17 (3.6)	0.28
Aortic regurgitation (≥ moderate)	14 (5.9)	24 (3.6)	0.63

Values are mean ± SD or n (%).

≥ moderate = at least moderate; AF = atrial fibrillation; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHADS-VASc score = Congestive heart failure, Hypertension, Age ≥75 years, Age 65-74 years, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Sex female; CHF = congestive heart failure; CVA = cerebrovascular accident; DOAC = direct oral anticoagulant; GFR = glomerular filtration rate; Hb = hemoglobin; ICH = intracerebral hemorrhage; IV = intravenous; LAAO = left atrial appendage occlusion; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SQ = subcutaneous; TIMI = Thrombolysis In Myocardial Infarction; VTE = venothromboembolic disorder.

DRT PREDICTORS AND RISK SCORE. Univariate analysis identified the following risk factors as potential risks for DRT formation: history of hypertension, diabetes, congestive heart failure, coronary

FIGURE 1 Distribution of LAA Morphology and LAAO Devices



(A) Left atrial appendage (LAA) morphology stratified by chicken-wing, windsock, cactus, cauliflower, and double-lobe. **(B)** Left atrial appendage occlusion (LAAO) device type stratified by Watchman, Watchman FLX, Amplatzer cardiac plug (ACP), Amplatzer Amulet, and other. DRT = device-related thrombus.

TABLE 2 Procedural Details

	DRT (n = 237)	Control (n = 474)	*P* Value
LAA parameters	(n = 168)	(n = 333)	
Morphology			
Chicken-wing	54 (32.1)	116 (34.8)	0.55
Windsock	64 (38.1)	129 (38.7)	0.89
Cactus	11 (6.6)	18 (5.4)	0.61
Cauliflower	23 (13.7)	35 (10.5)	0.29
Double lobe	13 (7.7)	22 (6.6)	0.64
Broccoli	1 (0.4)	6 (1.3)	
Other	2 (0.8)	7 (1.4)	
Dimensions			
TEE			
Diameter, mm	21.4 ± 5.6	20.4 ± 4.9	0.02
Length, mm	29.5 ±7.0	28.1 ± 6.2	0.06
CT			
Diameter, mm	25.2 ± 9.5	23.8 ± 9.6	0.36
Length, mm	31.8 ± 15.0	31.9 ± 14.4	0.80
TEE or CT			
Diameter, mm	22.3 ± 5.9	21.4 ± 5.6	0.04
Diameter >24 mm	52 ± 34.2	83 ± 28.2	0.19
Length, mm	30.7 ± 8.4	29.2 ± 7.8	0.06
Device size, mm	26.7 ± 3.7	26.1 ± 3.7	0.07
Contrast volume, mL	74.1 ± 59.4	73.5 ± 55.9	0.80
Number of recaptures	0.4 (0.9)	0.4 (1.0)	0.26
Recaptures, ≥1	56 (23.6)	96 (20.3)	0.30
Depth of LAAO implant, mm	12 ± 8.4	8.2 ± 6.5	0.0001
Depth of LAAO, ≥10 mm	105 (44.3)	138 (29.1)	0.0001
Procedural imaging			0.72
TEE	188 (79.3)	380 (80.2)	
ICE	21 (8.9)	46 (9.7)	
TEE + ICE	8 (3.4)	10 (2.1)	
Procedural complications (n = 644)	15 (6.3)	10 (2.1)	0.004
Pericardial effusion (n = 589)	8 (3.4)	3 (0.6)	0.01
Device embolization (n = 588)	1 (0.4)	0 (0.0)	0.33
Access site (n = 590)	6 (2.5)	7 (1.5)	0.38
Embolic event (n = 585)	2 (0.8)	0 (0.0)	0.11

Values are n (%) or mean ± SD.

CT = computed tomography; ICE = intracardiac echocardiography; LAA = left atrial appendage; TEE = transesophageal echocardiography; other abbreviations as in Table 1.

artery disease, stroke, venothromboembolic disorder, hypercoagulability disorders, left ventricular dysfunction, renal insufficiency, LAA diameter >24 mm, implantation depth >10 mm, nonparoxysmal AF, high-risk AF, pericardial effusion, and the presence of PDL as potential variables for predicting of DRT (Supplemental Table 4). Implementing these variables in a multivariable model yielded the following 5 predictors augmenting the risk of DRT: hypercoagulability disorder (OR: 17.50; 95% CI: 3.39-90.45), pericardial effusion (OR: 13.45; 95% CI: 1.46-123.52), renal insufficiency (OR: 4.02; 95% CI: 1.22-13.25), implantation depth >10 mm from the pulmonary vein limbus (OR: 2.41; 95% CI: 1.57-3.69) and nonparoxysmal AF (OR:1.90; 95% CI: 1.22-2.97) (**Figure 7**). Diabetes was noted as a protective factor against DRT formation, though this likely represents a spurious result. Given the large proportion of late DRT noted, we performed sensitivity analysis to clarify the differential risk factors for early versus late DRT. Accordingly, we dichotomized to early (<180 days) versus late DRT (>180 days), supporting a persistent effect for both hypercoagulability and deep implantation depth in both early and late DRT. Conversely late DRT was also predicted by hypertension and PDL, whereas early DRT was predicted by nonparoxysmal AF and pericardial effusion (Supplemental Table 5).

To generate a DRT risk score, these 5 DRT risk factors were normalized to integer values and incorporated into a DRT risk score (4 points for hypercoagulability disorder, 4 points for pericardial effusion, and 1 point for renal insufficiency, LAAO depth of implantation >10 mm from the pulmonary vein limbus, and nonparoxysmal AF). Summary scores were then calculated for each patient and dichotomized into low DRT risk score (1) and high DRT risk score (≥2) which yielded a 2.1-fold greater risk for high-risk patients when compared with those with no risk factor points (**Figure 8**). Alternatively, risk factors with 4 points were considered major risk factors, while those with 1 point were considered minor risk factors with the presence of either 1 major or 2 minor risk factors yielding a 2.1-fold increased risk of DRT formation (**Central Illustration**).

DISCUSSION

This largest-to-date multicenter dedicated LAAO-DRT registry documents confirmatory and novel findings. It confirms the association of DRT with major ischemic events, and the resolution of DRT with OAC treatment in most patients. It also identifies novel patient-specific and procedural factors that are associated with the development of DRT while synthesizing this into a clinical risk score to improve risk stratification (**Central Illustration**).

The clinical sequalae of DRT following LAAO remain the subject of debate. Our study demonstrates a 2-fold increased MACE rate driven by ischemic stroke. A recent real-world registry (EWOLUTION [Registry on Watchman Outcomes in Real-life Utilization]) with 34 DRT cases showed no

difference in the rate of ischemic stroke/transient ischemic attack between patients with LAAO with DRT and those without (1.7% vs 2.2%, respectively; $P = 0.80$) (12). Conversely, other studies have documented 3-fold (5), 4-fold (9), and up to 5-fold greater rates of ischemic events in those with DRT compared with in those without DRT (6). Although discerning the precise impact of DRT on ischemic outcomes remains inherently biased by variations in follow-up imaging practices, the persistent signal of increased ischemic events warrants attention. On diagnosis, patients are typically placed on more intensive antithrombotic agents to clear the thrombus and mitigate risk of embolic events as demonstrated in our analysis. This approach successfully clears thrombus in many cases with only a quarter of cases demonstrating persistent DRT presence in follow-up. Reassuringly, despite the bleeding risk of these patients, our studied cohort did not suggest an increase in bleeding rates with the treatment of DRT.

Predicting DRT remains a priority for the LAAO field, especially considering the increasing procedural volumes and its expansion to younger, lower-risk patients. Dukkipati et al (5) examined the LAAO arms of the landmark LAAO versus warfarin randomized trials and their nested registries, in which the incidence of DRT was 65 out of 1,735 cases (3.74%). These studies employed standardized regimens of aspirin and warfarin to 6 weeks, DAPT from 6 weeks to 6 months, and SAPT thereafter. In this setting, prior history of transient ischemic attack/stroke, permanent AF, left ventricular function, vascular disease, and LAA diameter were independent predictors of DRT (5). In another multicenter study by Fauchier et al (9), in which 26 of 469 patients (5.5%) developed DRT, advanced age and prior stroke were independently associated with DRT, whereas DAPT or OAC on discharge were protective from DRT. A study by Pracon et al (10) (n = 99, of whom 7 had DRT) suggested that deep device implant might be associated with a greater risk of DRT formation. Moreover, Korsholm et al (13) (n = 301, of whom 5 had DRT) supported these findings while noting the utility of both TEE and CT for detection. The small number of DRT cases in these studies significantly limited these predictive models, which was in part what inspired the design of our current registry. Our study collected information on 237 DRT cases from 37 centers worldwide along with control cases (1:2 fashion) from the same sites to enable for a multivariable analysis to identify predictors of DRT. In our LAAO-DRT registry, 5 independent risk factors for DRT were identified: hypercoagulability disorder, iatrogenic pericardial effusion, renal insufficiency, implantation depth >10 mm from the pulmonary ridge, and nonparoxysmal AF. Congestive heart failure, CHA_2DS_2-VASc score, prior stroke, PDL, and antithrombotic regimen on discharge were not independent predictors of DRT. These findings deserve more scrutiny.

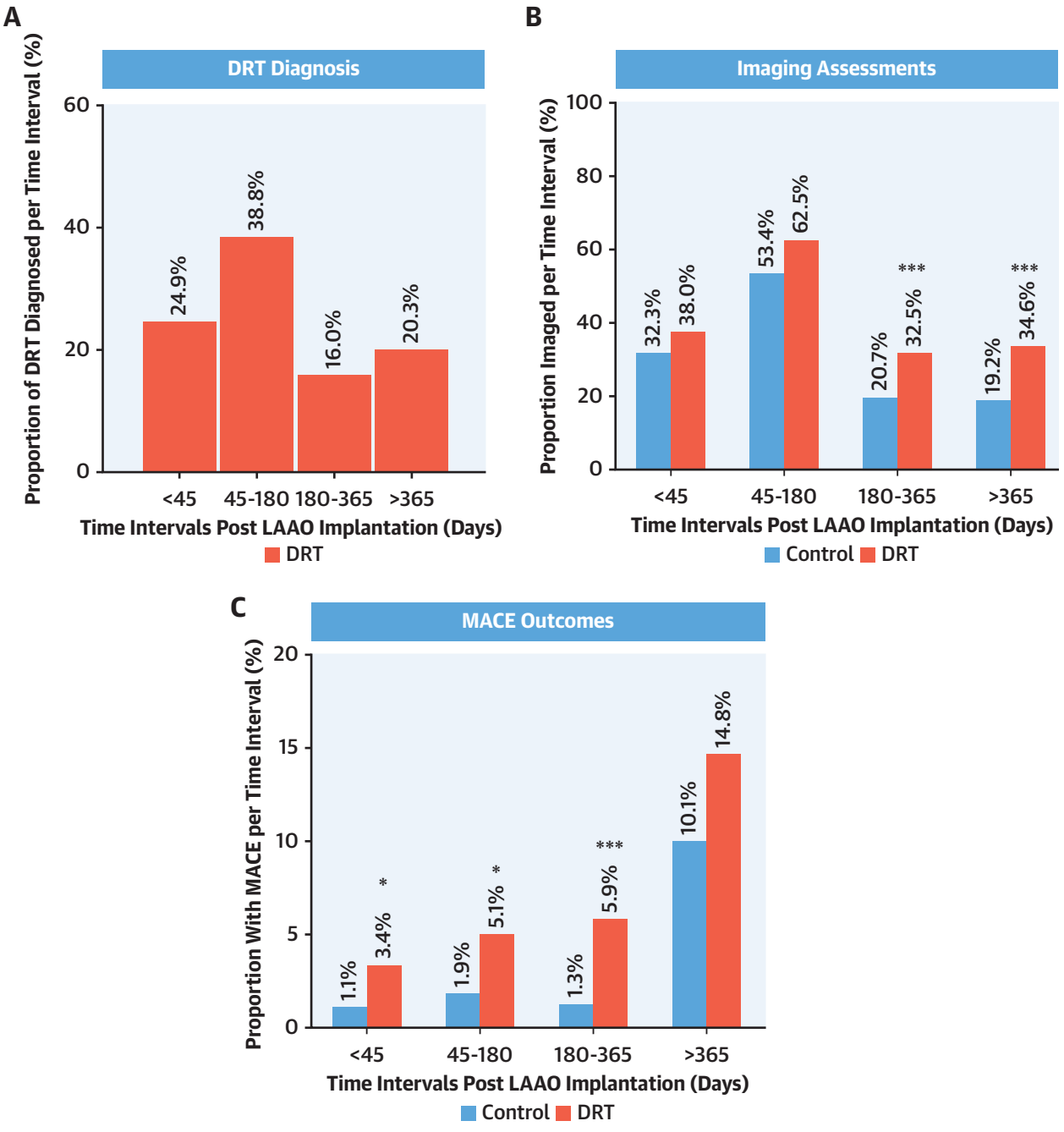
The sole independent modifiable factor from a technical perspective was the depth of implantation. Implantation depth has been previously described on the basis that residual exposed LAA aspects may still provide adequate stasis to promote thrombus formation (10) (**Figure 9**). Depth assessments are challenged by the varying anatomies, anatomical landmarks, measurement conventions, and device types (plug-type vs disk-lobe device). These data suggest that a depth measurement from the pulmonary vein limbus may be helpful in standardizing the assessment of implant as it relates to prediction of DRT while advancing imaging modalities aim to further improve assessment particularly in the setting of DRT (**Figure 10**). In fact, pulmonary limbus coverage with lobe-and-disk devices has demonstrated reduced rates of DRT following LAAO (14). The association of

TABLE 3 Outcomes

	DRT (n = 237)	Control (n = 474)	*P* Value
Clinical outcomes			
Time to follow-up, y	1.6 (1.0-2.9)	1.8 (0.9-3.0)	0.76
MACEs (n = 709)	70 (29.5)	68 (14.4)	0.0001
Death (n = 672)	36 (15.2)	55 (11.6)	0.19
Ischemic stroke (n = 597)	40 (16.9)	17 (3.6)	0.0001
Systemic embolism (n = 611)	7 (3.0)	3 (0.6)	0.02
Stroke or systemic embolism (n = 653)	46 (20.9)	19 (4.4)	0.0001
Bleed—any (n = 654)	29 (13.3)	43 (9.9)	0.19
TIMI major	16 (6.8)	23 (4.9)	
TIMI minor	10 (4.2)	17 (3.6)	
Other	3 (1.3)	3 (0.7)	
ICH (n = 610)	1 (0.5)	3 (0.7)	1.00
Recurrent bleeding (n = 587)	14 (7.3)	18 (4.6)	0.18
Device outcomes			
Device migration (n = 623)	6 (2.7)	0 (0.0)	0.002
PDL - Overall	82 (34.6)	118 (26.1)	0.005
Diagnosed at implantation	20 (8.4)	23 (4.9)	0.05
Diagnosed in follow-up	79 (33.3)	107 (22.6)	0.003
PDL size, mm			0.51
<3	42 ± 17.7	74 ± 15.6	
3-5	29 ± 12.2	38 ± 8.0	
>5	8 ± 3.4	9 ± 1.9	
Largest PDL size, mm	1.8 ± 2.0	1.2 ± 1.6	0.003
Proportion with multiple PDLs, ≥1	81 (34.2)	118 (24.9)	0.01

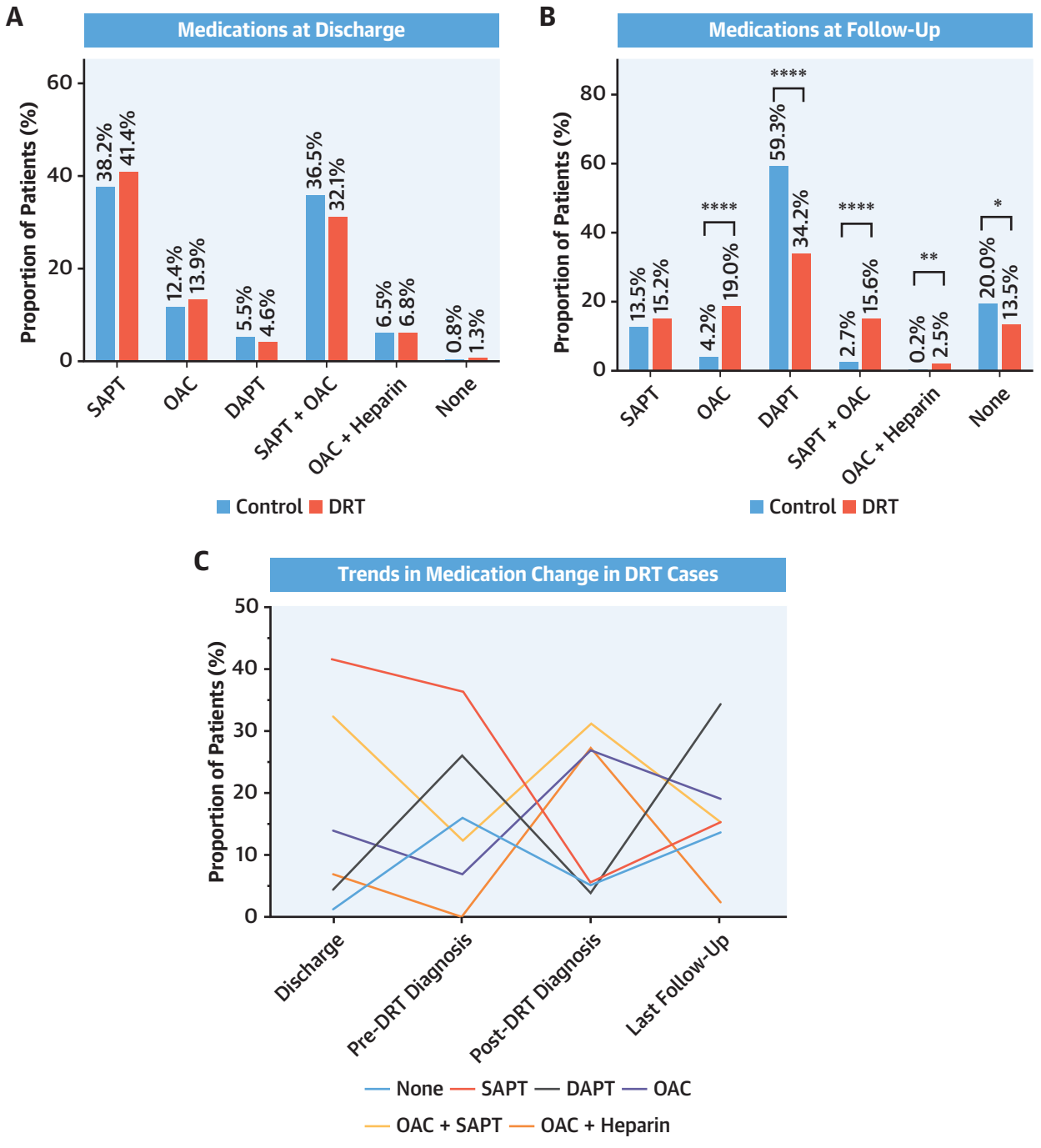
All values are median (interquartile range), n (%), or mean ± SD. IQR = interquartile range; MACE = major adverse cardiac event; PDL = peridevice leak; other abbreviations as in Table 1.

FIGURE 2 Temporal Analysis of DRT Diagnosis, Imaging, and MACE



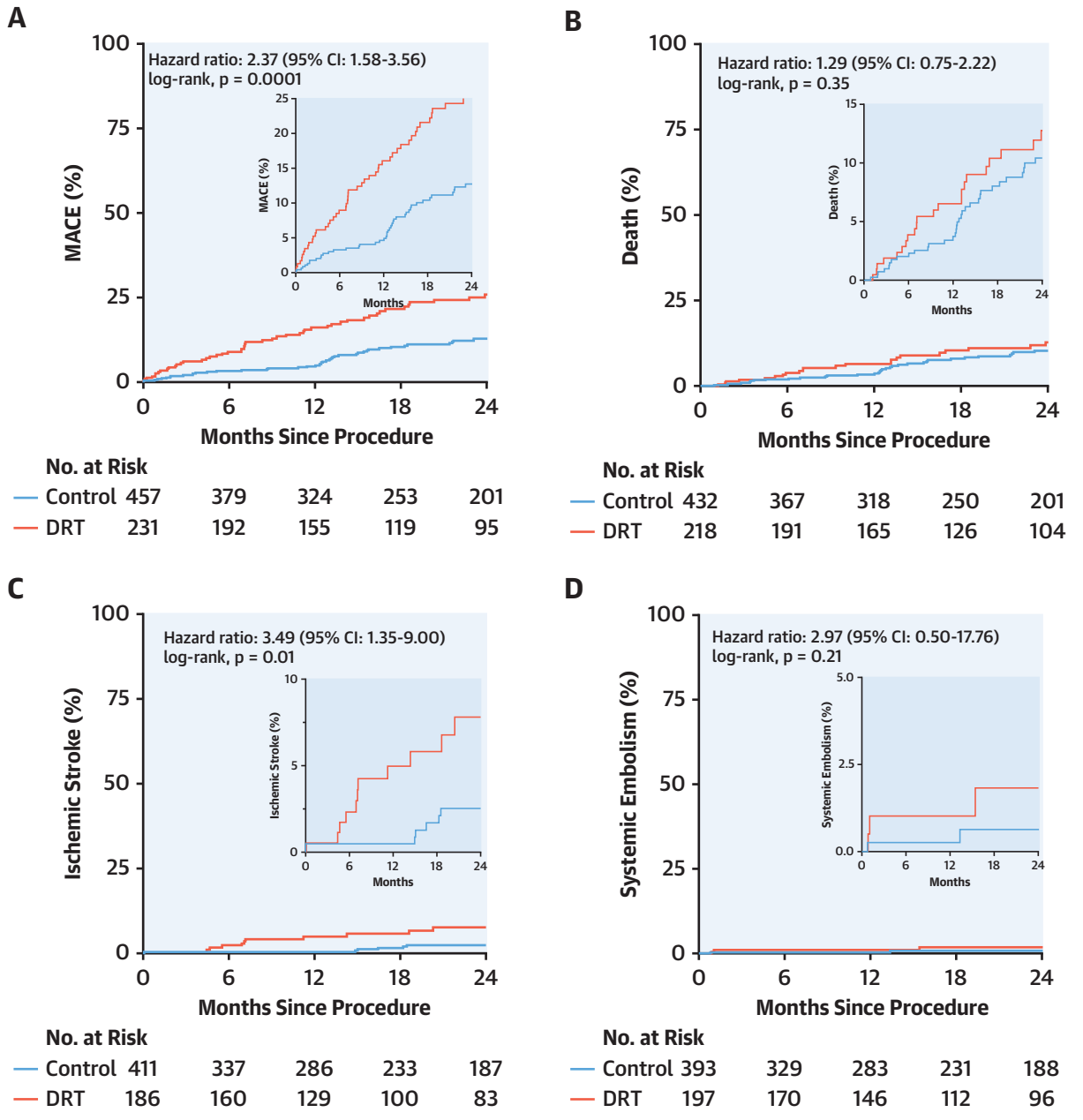
(A) Of the 237 reported DRT cases, 59 (24.9%), 92 (38.8%), 38 (16.0%), and 48 (20.3%) were reported at time intervals of 0 to 45, 45 to 180, 180 to 365, and >365 days, respectively. **(B)** Relative proportion of the control subjects and patients with DRT that underwent imaging (computed tomography or transesophageal echocardiography) during predefined follow-up intervals. **(C)** Proportion of control subjects and patients with DRT that experienced a major adverse cardiac event (MACE) during predefined follow-up intervals. *$P < 0.05$, ***$P < 0.001$. Abbreviations as in Figure 1.

FIGURE 3 Post-LAAO Medication Management



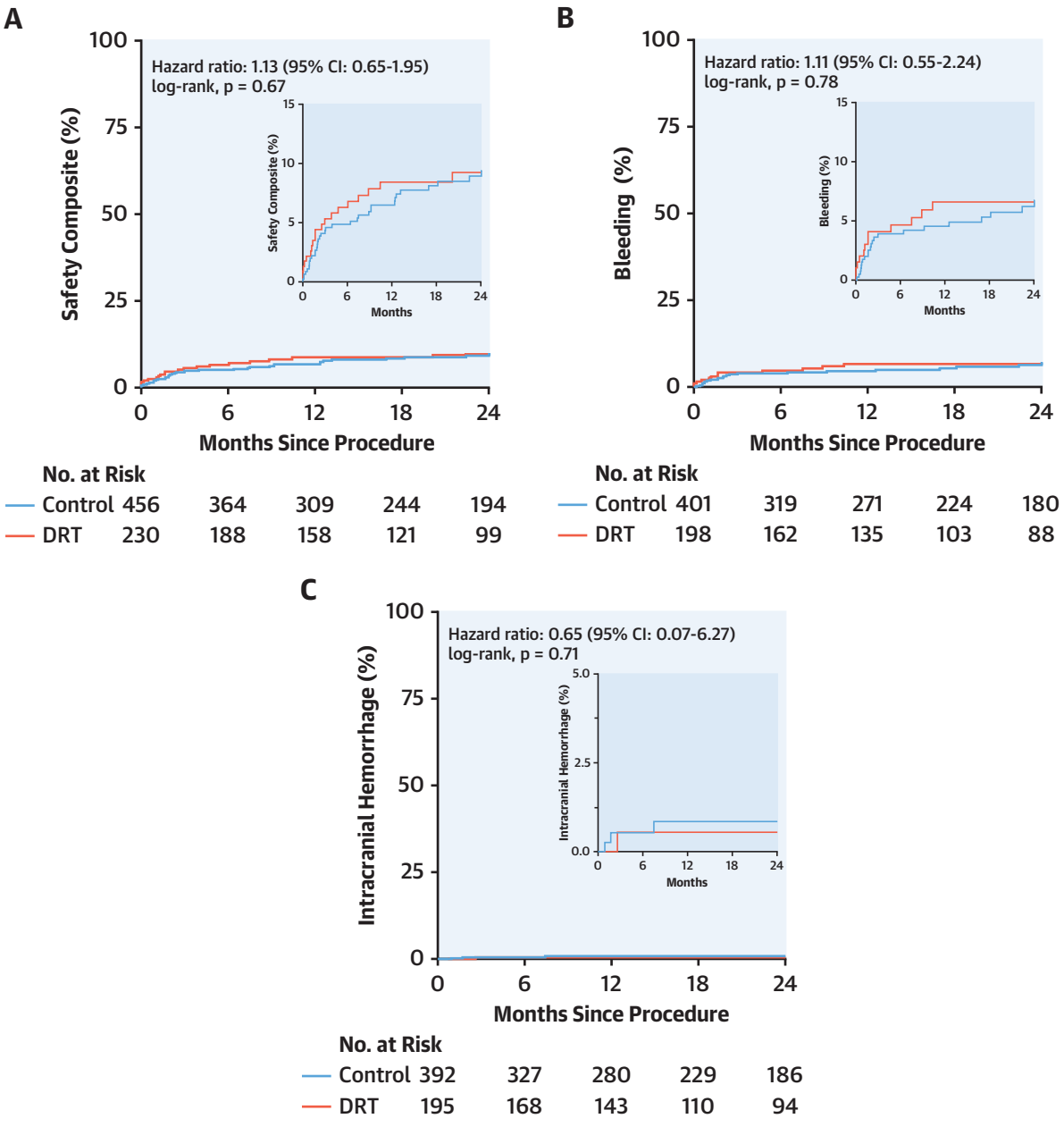
(A) Medication at discharge stratified by control and DRT cases. **(B)** Medication at last known follow-up stratified by control and DRT cases. Differences between control and DRT cases at discharge and follow-up were analyzed by chi-square test. **(C)** Trends in medication change in DRT cases from discharge, pre-DRT diagnosis, immediately post-DRT diagnosis, and last known follow-up. *$P < 0.05$, **$P < 0.01$, ****$P < 0.0001$. DAPT = dual antiplatelet therapy; OAC = oral anticoagulation; SAPT = single antiplatelet therapy; other abbreviations as in Figure 1.

FIGURE 4 Clinical Outcomes Following LAAO



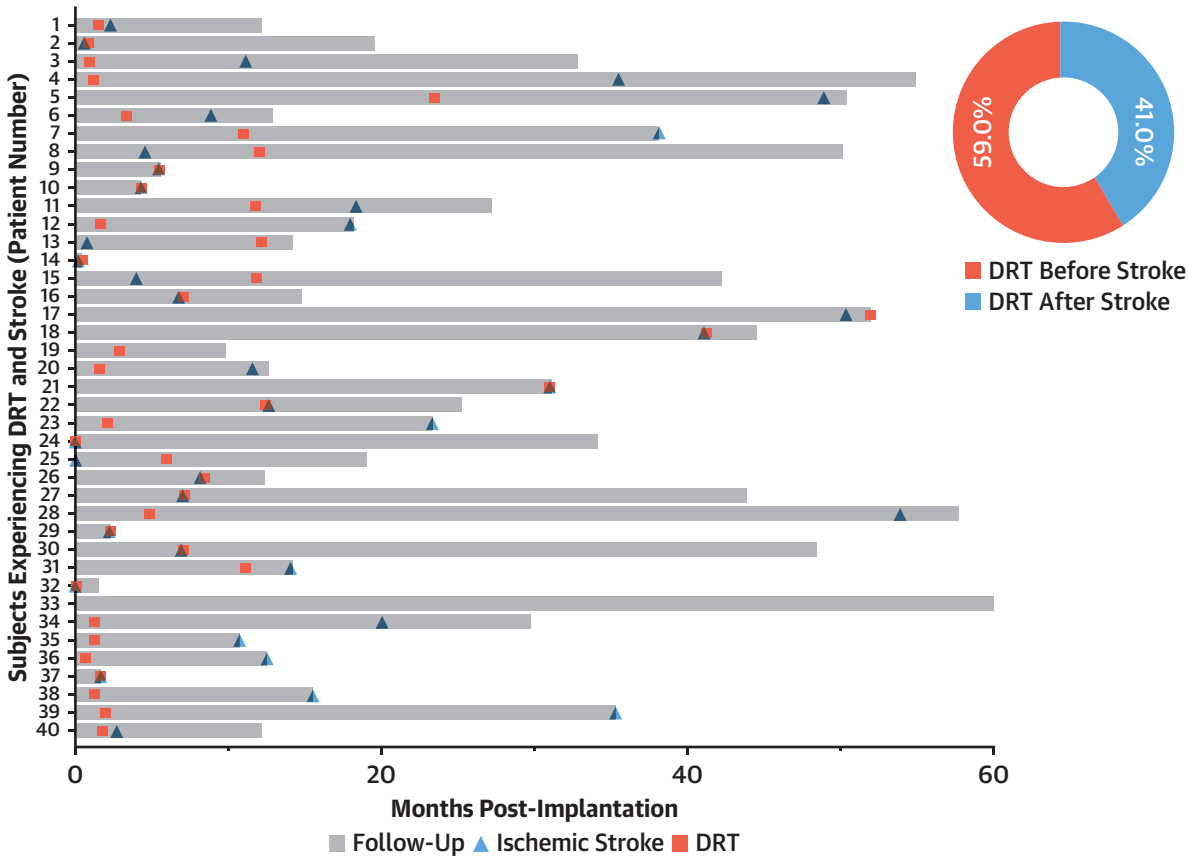
Outcomes stratified by DRT **(red)** and non-DRT control **(blue)** cases. **(A)** Patients with cumulative incidence of MACEs among patients who underwent LAAO. DRT was associated with increased rates of MACEs (HR: 2.37; 95% CI: 1.58-3.56; $P = 0.0001$). **(B)** Cumulative incidence of mortality among patients who underwent LAAO. No difference in mortality was observed between DRT and control cases (HR: 1.29; 95% CI: 0.75-2.22; $P = 0.35$). **(C)** DRT was associated with increased rate of ischemic stroke (HR: 3.49; 95% CI: 1.35-9.00; $P = 0.01$). **(D)** No difference in systemic embolism rates were observed between DRT and control cases (HR: 2.97; 95% CI: 0.50-17.76; $P = 0.21$). Kaplan-Meier curves were generated and compared by log-rank test and evaluated using Cox proportional hazards model. $P < 0.05$ is considered statistically significant. Abbreviations as in Figures 1 and 2.

FIGURE 5 Bleeding Outcomes Following LAAO



Outcomes stratified by DRT **(red)** and control **(blue)** cases following LAAO. **(A)** Patients with cumulative incidence of safety composite (bleeding and intracerebral hemorrhage) among patients who underwent LAAO. No difference in safety composite outcome was observed between DRT and control cases (HR: 1.13; 95% CI: 0.65-1.95; $P = 0.67$). **(B)** No difference in bleeding was observed between DRT and control cases (HR: 1.11; 95% CI: 0.55-2.24; $P = 0.78$). **(C)** No difference in intracerebral hemorrhage was observed between DRT and control cases (HR: 0.65; 95% CI: 0.07-6.27; $P = 0.71$). Kaplan-Meier curves were generated and compared by log-rank test and evaluated using Cox proportional hazards model. $P < 0.05$ is considered statistically significant. Abbreviations as in Figure 1.

FIGURE 6 Temporal Analysis of DRT and Ischemic Strokes

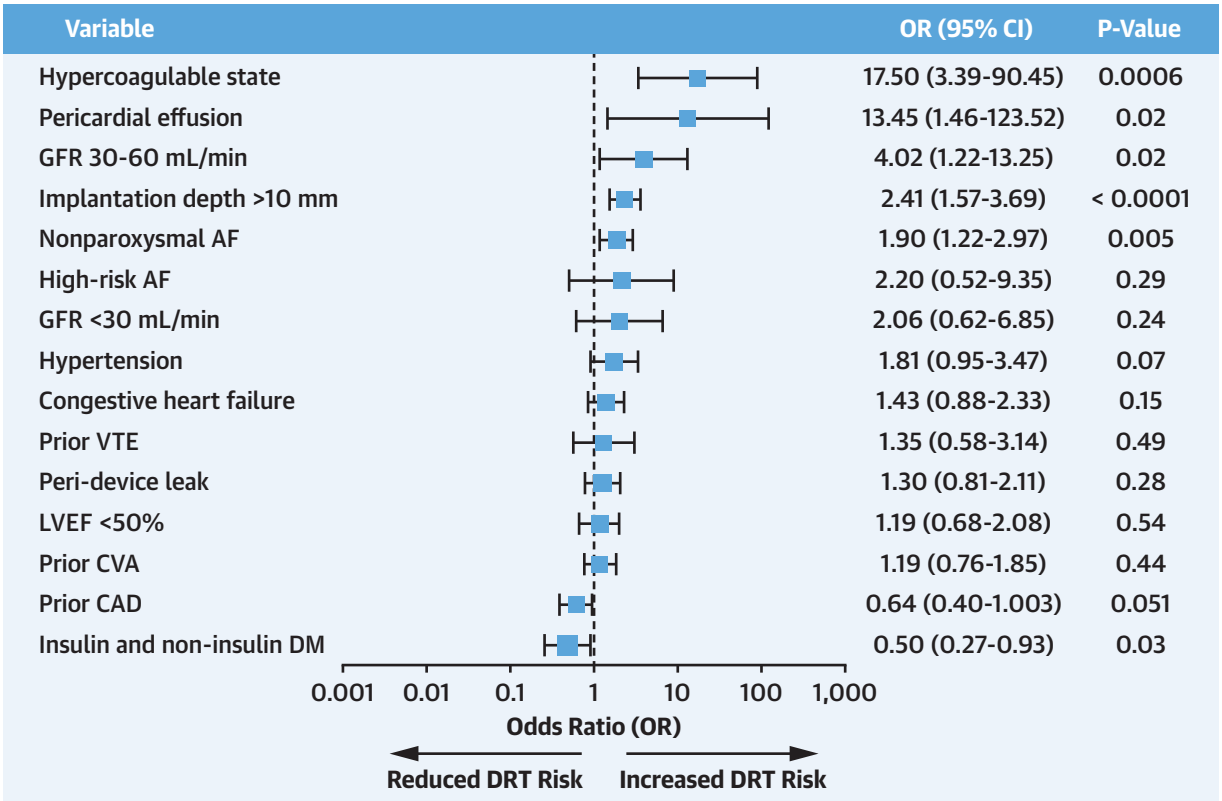


Subset of patients who experienced device-related thrombus (DRT) and stroke within the cohort included. **Gray lines** denote duration of follow-up for each subject. Time of DRT diagnosis **(red squares)** and ischemic stroke **(blue triangles)** were then indicated in the follow-up course. Inset chart summarizing temporal relationship between DRT and stroke diagnoses. Note: Patient 33 had prolonged follow-up and was truncated from chart for improved clarity with stroke at 93.7 months, DRT at 129.6 months, and last follow-up at 154.1 months.

certain clinical risk factors with DRT is intuitive. For example, long-standing permanent AF is a harbinger of progressive atrial myopathy, which has been associated with an increased risk of embolic events in prior AF studies (15–17). Similarly, hypercoagulopathy is a known risk factor for both venous and arterial thrombotic complications. Moreover, iatrogenic periprocedural pericardial effusions are likely to lead to acceptance of suboptimal technical results and diminished use of periprocedural antithrombotic agents. Although the impact of nonmodifiable DRT risk factors on practice need to be studied, it is reasonable to assume that their identification might be useful in guiding patient-specific decision making and perhaps in device selection, implantation, and postprocedural management. The association of renal insufficiency with DRT requires further exploration, with this cohort potentially exhibiting global vascular dysfunction that predispose them to DRT and other thrombotic complications (18).

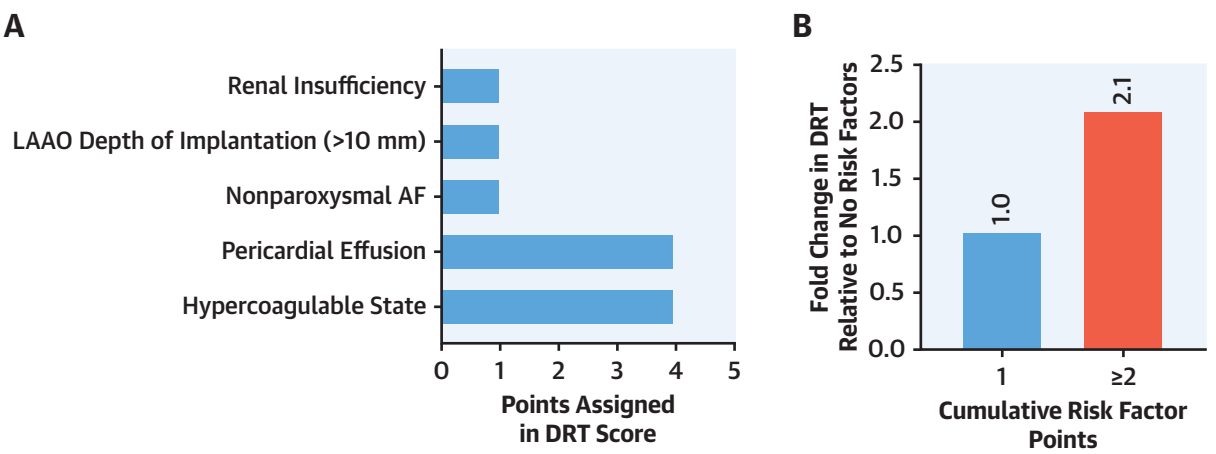
Notably, other risk factors that can logically be perceived as potential contributors to DRT did not correlate with DRT in this study. For example, PDL may contribute to DRT via direct extension of thrombus behind the device, flow stasis, abnormal healing responses, and even device migration with subsequent malpositioning (19). Although PDL was noted at higher frequency in the DRT cohort,

FIGURE 7 Predictors of DRT Following LAAO



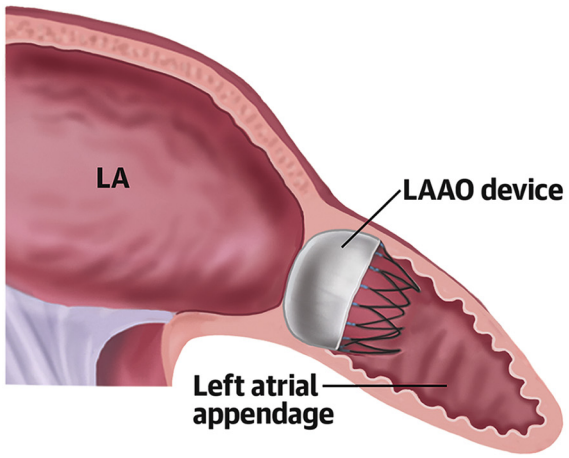
Variables identified following univariable logistic regression of $P < 0.20$ included in the final multivariable logistic regression model. Multivariable analysis data are presented as odds ratios (ORs) with corresponding 95% CIs. $P < 0.05$ is considered statistically significant. AF = atrial fibrillation; CAD = coronary artery disease; CVA = cerebrovascular accident; DM = diabetes mellitus; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; VTE = venothromboembolic disorder; other abbreviations as in Figure 1.

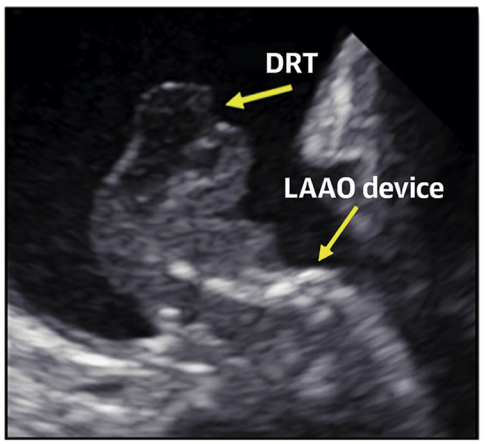
FIGURE 8 DRT Risk Score



(A) To generate a DRT risk score, 1 point was assigned for renal insufficiency, implantation depth >10 mm from the pulmonary vein limbus, and nonparoxysmal atrial fibrillation, while 4 points were assigned to iatrogenic pericardial effusion and hypercoagulability state. **(B)** DRT risk score was categorized into none (0 point), low risk (1 point) and high risk (>2 points) revealing a 1.0-fold (low risk) and 2.1-fold increased risk of DRT formation in those designated high risk when compared with those with no DRT risk factors present. Abbreviations as in Figures 1 and 7.

CENTRAL ILLUSTRATION DRT Following LAAO





Major Risk Factors

- latrogenic pericardial effusion
- Hypercoagulable state

Minor Risk Factors

- Deep LAAO implant (>10mm from pulmonary ridge)
- Renal insufficiency
- Non-paroxysmal AF

1 major risk factor

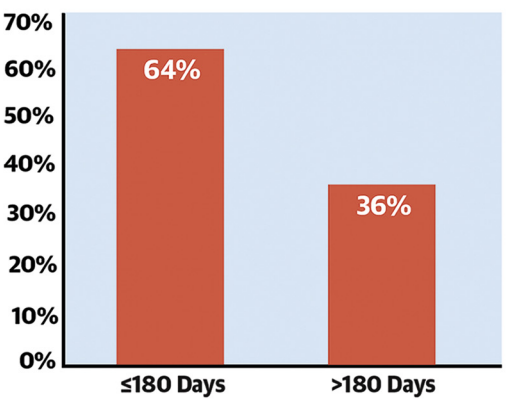
OR

2 minor risk factors

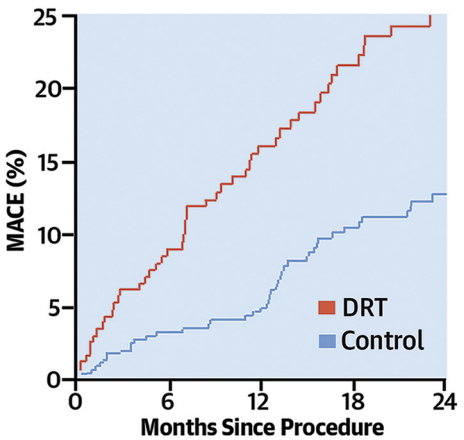
2.1-fold

Risk of Device Related Thrombus (DRT)

Timing of DRT Diagnosis Post LAAO



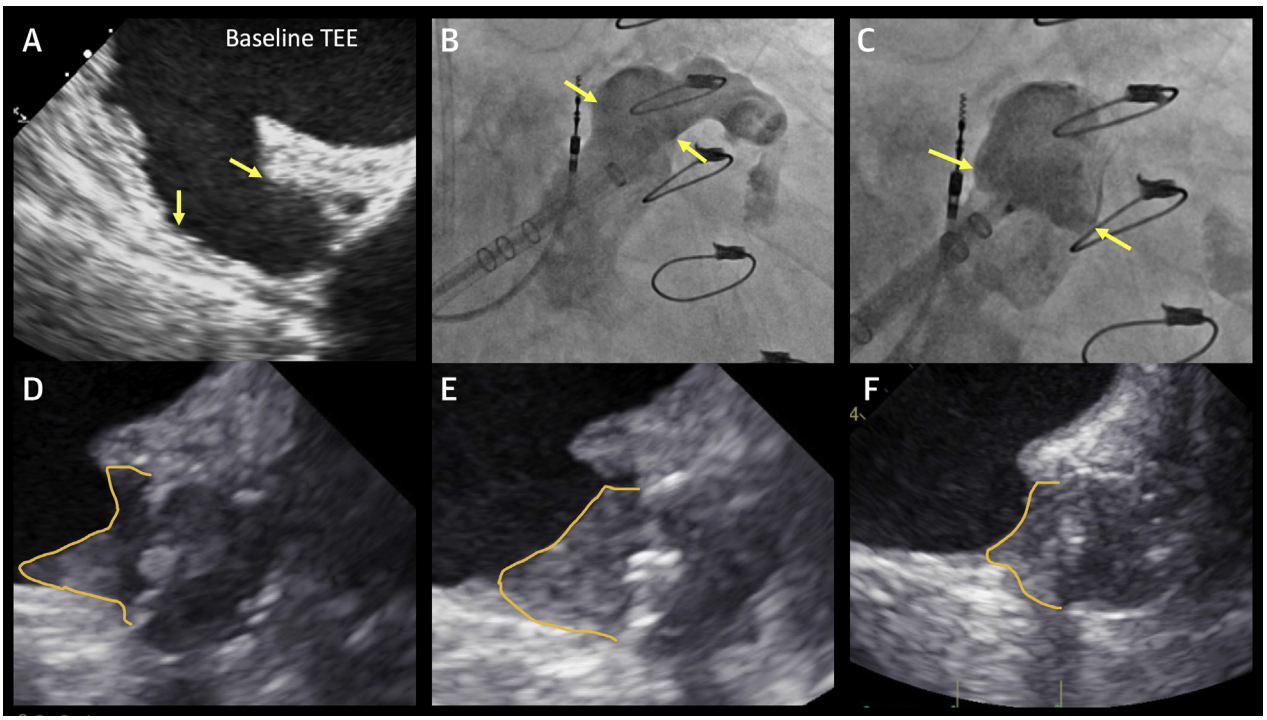
Outcomes of LAAO



Simard, T. et al. J Am Coll Cardiol. 2021;78(4):297-313.

Following left atrial appendage occlusion (LAAO) the presence of 1 major risk factor or 2 minor risk factors leads to a 2.1-fold increased risk of device-related thrombus (DRT) compared with those with no risk factors for DRT. The majority of DRT (64%) is diagnosed ≤180 days following procedural implant and is associated with an increased risk of major adverse cardiovascular events (MACEs). AF = atrial fibrillation; LA = left atrium.

FIGURE 9 Deep Implantation of LAAO Device With Subsequent Persistent DRT

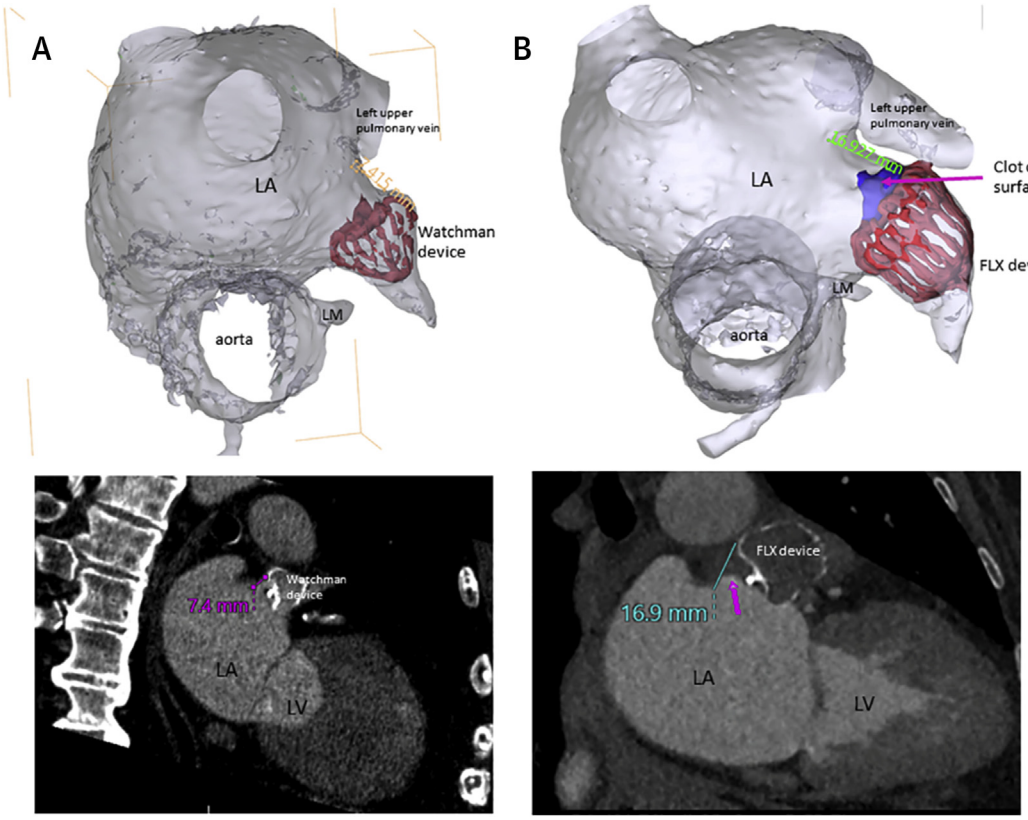


(A) Baseline transesophageal echocardiography (TEE). **(B)** Baseline angiography. **(C)** LAAO implant position. **Yellow arrows** denote final LAAO device face position with deep implantation (depth of ~20 mm on mitral valve aspect and ~10 mm on pulmonary ridge aspect of device). Post-implant DRT formation demonstrated by TEE at **(D)** 45 days post-implant; **(E)** 6 months post-implant while on DAPT; **(F)** 1 year with organized thrombus. **Yellow lines** denote atrial border of DRT on LAAO device. Abbreviations as in Figures 1 and 3.

multivariable analysis did not support it as an independent predictor of DRT. This is likely because of the confounding issue of augmenting OAC and imaging frequency when DRT is detected, thereby inadvertently detecting PDLs. Another key observation was that the medical regimen at discharge following LAAO did not affect the presence of DRT. Although counterintuitive, this is in keeping with the findings of several prior studies and a large meta-analysis including >12,000 patients (6). Certainly, both patient- and procedural-level factors should be considered when assessing the risk of DRT formation. Additional studies are needed to further understand the contributions of patient risk profile, device material, implantation techniques, and DRT considering the rapidly evolving landscape of LAAO devices and procedural practices.

The future of LAAO is dependent on the assurance of its long-term safety considering the preventative nature of the procedure. DRT remains an important unresolved issue with LAAO and has been the center of increasing attention in the last few years. Engineering efforts proposed that DRT is mostly a device design and material issue, with efforts to provide several device-specific solutions to mitigate the risk of DRT. These include attempting to minimize the exposed metal in the LAA (eg, Watchman FLX) or introducing antithrombotic materials to next-generation devices. The success of these strategies in reducing the incidence of DRT remain to be discerned although preliminary data from Watchman FLX are promising (20). Our study suggests that with current LAAO technology, patient and procedural factors may be an important contributor to the occurrence of DRT. Whether those factors will remain independently impactful with future device designs remain to be seen. Nonetheless, we speculate that mitigating the

FIGURE 10 CT and Computer-Aided Design Evaluation of Post-LAA CT



Two distinct patients are presented. **(A)** Patient 1: without clot on the atrial surface of the Watchman device with a pulmonary ridge to atrial surface distance of 7.4 mm. **(B)** Patient 2: with clot on the atrial gutter after a deeper Watchman FLX implant, with a pulmonary ridge to atrial surface distance of 16.9 mm. **Pink arrows** denote DRT location. CT = computed tomography; LA = left atrium; LM = left main; LV = left ventricle.

risk of DRT will require improvements in risk stratification, device design, and implantation techniques.

STUDY LIMITATIONS. DRT diagnosis, patient risk factors, and subsequent events were self-reported, and not standardized or independently adjudicated by core laboratories. Centers included in this report were those reporting at least 1 case of DRT during their cumulative experience, leading to potential overestimation of DRT incidence and selection bias with respect to the centers reported. There was considerable variability in the postimplant imaging regimens employed by various centers, contributing to variability in DRT detection timelines. Moreover, the lower incidence of ischemic events in the control cohort may reduce the probability of detecting asymptomatic DRT. The cohort is composed primarily of Watchman devices, limiting the broad applicability of these results to all LAAO devices. The relatively large time span over multiple centers with varying operator experience introduces additional bias with respect to device, technical, and center expertise, not necessarily reflecting contemporary device and operator practice.

CONCLUSIONS

DRT following LAAO is associated with increased rates of ischemic events. Patient and procedural risk factors can predict DRT, aiding in risk stratification and optimization of procedural techniques and post-procedural management.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

DRT occurs in ~5% of cases following LAAO, and is associated with an increased risk of ischemic events and MACE. Hypercoagulability disorders, renal insufficiency, non-paroxysmal AF, and device implantation depth >10 mm from the pulmonary vein limbus were more important predictors of DRT than the antithrombotic drug regimen employed for prophylaxis was.

TRANSLATIONAL OUTLOOK: Further research is needed to refine risk stratification for DRT in patients undergoing LAAO and assess the impact of various aspects of periprocedural management on clinical outcomes.

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KEY WORDS ACP, Amplatzer cardiac plug, Amulet, device-related thrombus, DRT, LAAO, left atrial appendage occlusion, Watchman, Watchman FLX

APPENDIX For a supplemental figures and tables, please see the online version of this paper.