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FOCUS ON LEFT ATRIAL APPENDAGE OCCLUSION

Incidence, Characterization, and Clinical Impact of Device-Related Thrombus Following Left Atrial Appendage Occlusion in the Prospective Global AMPLATZER Amulet Observational Study

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) recognize the potential clinical consequences of DRT following LAAO; 2) understand potential clinical and procedural risk factors for the occurrence of DRT; and 3) appreciate the 1-year incidence of DRT with the Amulet device in a large prospective, multicenter observational study and compare this incidence with previous reports.

CME/MOC/ECME Editor Disclosure: *JACC: Cardiovascular Interventions* CME/MOC/ECME Editor Michael C. McDaniel, MD, has reported that he is a Penumbra-Investigator on the EXTACT-PE trial.

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Incidence, Characterization, and Clinical Impact of Device-Related Thrombus Following Left Atrial Appendage Occlusion in the Prospective Global AMPLATZER Amulet Observational Study

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ABSTRACT

OBJECTIVES This study sought to report the incidence, characteristics, and clinical impact of device-related thrombus (DRT) following left atrial appendage occlusion (LAAO) with the AMPLATZER Amulet device (Abbott, Plymouth, Minnesota).

BACKGROUND DRT is a potential serious complication of LAAO, but the incidence and clinical impact of DRTs in a real-world setting are not well characterized.

METHODS A total of 1,088 patients were enrolled in a multicenter prospective study and followed for 1 year. All events were adjudicated by an independent committee, including the presence of DRT. Patients with DRT were reviewed for suboptimal device implantation and characterization of DRT formation. Multiple Cox regression was performed to identify predictors of DRT formation.

RESULTS Device implantation was successful in 1,078 (99%) patients, with 1-year follow-up completed in 96.3% of patients. A total of 18 DRTs occurred in 17 patients (1.7%/year), as a second DRT developed following complete resolution of an initial DRT in 1 patient. The left upper pulmonary vein ridge was not covered by the Amulet disc in 82% of DRT patients, indicating suboptimal implantation, with most thrombus developing in the untrabeculated area of the LAA ostium between the pulmonary vein ridge and the upper edge of the disc. Three (18%) DRT patients had an ischemic stroke, all within 3 months of DRT diagnosis. Patients with a DRT were at a greater risk for ischemic stroke or transient ischemic attack compared with non-DRT patients (hazard ratio: 5.27; 95% confidence interval: 1.58 to 17.55; $p = 0.007$). Larger LAA orifice width was a predictor of DRT formation (hazard ratio: 1.09; 95% confidence interval: 1.00 to 1.19; $p = 0.04$).

CONCLUSIONS Following LAAO with the AMPLATZER Amulet device, DRT was observed infrequently. Although the presence of DRT was associated with an increased rate of ischemic stroke or transient ischemic attack as compared with patients without DRT, the large majority of DRT patients (82%) did not experience any ischemic neurologic events. (J Am Coll Cardiol Intv 2019;12:1003–14) © 2019 by the American College of Cardiology Foundation.

Percutaneous left atrial appendage occlusion (LAAO) is an effective therapy to reduce the risk of ischemic stroke without the need for long-term oral anticoagulation (OAC) in select patients with nonvalvular atrial fibrillation (AF). Formation of a device-related thrombus (DRT) is a potential complication of LAAO, especially early after implant, before endothelization of the device. The incidence of DRT following LAAO ranges from <2% (1,2) to 25% (3), but is generally reported to be 2% to 5% (4–12) in larger cohorts. Predictors of DRT formation following LAAO include older age (3), history of ischemic stroke or transient ischemic attack (TIA) (3,5), LAA width (5), reduced left ventricular ejection fraction (LVEF) (5,13), and permanent AF (5). However, design differences between the 2 most commonly used LAAO devices, the WATCHMAN (Boston Scientific, Marlborough, Massachusetts) and the AMPLATZER Amulet (Abbott, Plymouth, Minnesota), as well as differences between the manufacturer recommended post-LAAO medication regimen and the regimen observed in real-world clinical practice, limit the generalizability of DRT reports.

The objective of the present study is to summarize the incidence, characterization, and clinical impact of DRTs following LAAO from the large prospective, multicenter, global Amulet Observational Study.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

APT = antiplatelet therapy

CEC = clinical events committee

CI = confidence interval

CT = computed tomography

DRT = device-related thrombus

HR = hazard ratio

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

OAC = oral anticoagulation

PV = pulmonary vein

TEE = transesophageal echocardiography

METHODS

This analysis used the 1-year follow-up data of the prospective Amulet Observational Study (NCT02447081) (14). Study visits occurred at discharge, 1 to 3 months, 6 months, and 1 year following LAAO. A clinical events committee (CEC) adjudicated all serious adverse events, including the presence of DRT. DRT was defined as an echocardiographic or computed tomography (CT) density on the left atrial aspect of the device: 1) not explained by imaging artifact; 2) inconsistent with normal healing; 3) visible in multiple transesophageal echocardiogram (TEE) or CT planes; and 4) in contact with the device. When a participating site observed a DRT, source documentation was submitted to the CEC, and the CEC independently adjudicated the presence of the DRT. Clinical event reporting follows the Munich Consensus Document, including reporting deaths adjudicated by the CEC as an unknown cause conservatively as cardiovascular deaths (15).

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The protocol required a transthoracic echocardiogram before discharge, a TEE 1 to 3 months after LAAO, and a TEE if a stroke or transient ischemic attack (TIA) occurred. Additional echocardiograms or CTs, acquired by site standard of care, may have been performed and presence of DRT reported to the CEC, if applicable. Residual flow around the device and presence of DRT were assessed on procedural and follow-up echocardiograms by a core laboratory (MedStar Health Research Institute, Washington, DC), blinded to clinical condition.

Additional focused echocardiographic analysis was performed on implant and follow-up studies of DRT patients. The position of the Amulet lobe was defined as appropriate if located within 10 to 15 mm distal to LAA orifice, too proximal if the distal part of the lobe was located <10 mm from the LAA orifice, and too distal if the proximal part of the lobe was located more than 15 mm from the LAA orifice. The presence of an adequate sizing of the Amulet device during implantation or follow-up was based on the visual assessment of the compression of the lobe. Adequate device compression was reflected by the lobe depicting a "tire-like" shape on TEE and associated with concavity of the Amulet disc (reflecting the adequate anchorage of the lobe within the LAA neck). The device was considered as undersized if the lobe had a "square-like" shape, with a low level of compression, and poor or absent disc concavity (16,17). DRT was defined as diffuse if >50% of the disc surface was covered by thrombus and mobile when clear motion was observed in at least 3 sequential frames (10). DRT was defined as laminar (basal length > height) or pedunculated (height > basal length), and with smooth versus irregular contours. Only echocardiograms from patients with DRT over the first year underwent this subanalysis.

The protocol recommended patients take aspirin ≥6 months post-LAAO and clopidogrel per standard of care. The antithrombotic medication regimen and duration following observation of a DRT was at the clinician's discretion.

STATISTICAL ANALYSIS. Baseline and procedural characteristics and medications were summarized using descriptive statistics. The Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables were used to identify differences in characteristics between patients with and without DRT. Annualized rates were calculated for stroke, TIA, and major bleeding events, and compared between DRT and non-DRT patients via a Poisson regression model. The incidence rate of DRT was calculated using Kaplan-Meier method. Two composite clinical outcomes are reported: 1) cardiovascular (CV) death, ischemic stroke, or TIA; and 2) ischemic stroke or TIA. Composite clinical outcomes were counted irrespective of their temporal relationship to the DRT diagnosis and were graphed using Kaplan-Meier method. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the 2 composite outcomes, adjusting for baseline CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category) and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) scores. Cox proportional hazards regression was used to identify variables associated with DRT formation. Variables with univariate p values <0.20 were subsequently included in the multiple regression analysis. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for analysis and STATA/SE 15.1 (StataCorp, College Station, Texas) for graphing.

RESULTS

PATIENT CHARACTERISTICS. A total of 1,088 patients were enrolled, with successful device implantation in 1,078 patients. The 10 patients not receiving an Amulet device were withdrawn per the protocol,

with no clinical events observed. Eighteen DRT were observed in 17 patients within the first year of follow-up, yielding a rate of 1.7%/year. One patient had a DRT form after complete resolution of an initial DRT. Patient follow-up at 1-year was 96.3% (14), resulting in 16.4 and 985.0 patient-years of follow-up for those with and without DRT, respectively. Echocardiograms were acquired in 925 of the 1,018 (90.9%) patients undergoing a 1- to 3-month visit. Patients with DRT were older (79.4 ± 7.1 years of age vs. 75.1 ± 8.5 years of age; p = 0.03) (Table 1). The 2 groups were similar in terms of the proportion of patients in AF at the time of implant, with congestive heart failure, and having a previous stroke or TIA. Patients with and without DRT were both at high risk for major bleeding based on history of major bleeds (65% vs. 72%), HAS-BLED score (3.1 ± 0.8 vs. 3.3 ± 1.1), and contraindication to OAC (82% vs. 83%). The average LAA ostial width was larger (24.9 ± 4.4 mm vs. 22.3 ± 5.0 mm; p = 0.02) in patients with a DRT.

ANTITHROMBOTIC TREATMENT. In patients with DRT, the discharge medication was dual antiplatelet therapy (APT) in 59% of patients, single APT in 12% of patients, and anticoagulation therapy (OAC or low-molecular-weight heparin) in 29% of patients (Table 1). Patients without DRT were discharged on dual APT, single APT, and anticoagulation therapy in 58%, 23%, and 18% of cases, respectively. At the time of DRT diagnosis, the antithrombotic treatment consisted of single APT in 8 (44%), dual APT in 6 (33%), anticoagulation in 2 (11%), and no antithrombotic medications in 2 (11%) cases. Following DRT diagnosis, patients received anticoagulant treatment in 83% of cases.

CLINICAL OUTCOME AND PREDICTORS OF DRT. Clinical outcomes, through 1-year post-LAAO, are shown in Table 2. The relationship of DRT diagnosis, thromboembolic events, and antithrombotic medication utilization is shown in Figure 1. A DRT previously reported (14) as being observed on day 362 (243 days following ischemic stroke) was found to be visualized on a TEE 210 days post-LAAO (91 days post-stroke), as additional data was reviewed for this subanalysis.

Three of the 17 DRT patients had an ischemic stroke, corresponding to an annualized rate of 18.3%. In these patients, DRT was observed on the same day, 24 days before, and 91 days after the stroke event. No TIAs were observed in patients with DRT. There were 26 ischemic strokes in 24 of the non-DRT patients, yielding an annualized rate of 2.6%/year. All ischemic strokes in patients with DRT occurred >7 days after implant, while 22 of the 26 ischemic strokes in patients without DRT occurred >7 days after implant. Nine TIAs (0.9%/year) were observed in patients without DRT, all occurring >7 days after implant.

All-cause mortality rates were 14.4% and 8.3%, based on 2 and 86 deaths for patients with and without DRT, respectively. DRT patients died 12 and 51 days after DRT diagnosis, both due to cardiovascular causes complicated by multiorgan failure. Neither of the 2 DRT patients that died suffered an ischemic stroke.

TABLE 1 Characteristics of Patients With or Without Device-Related Thrombus

	DRT Within First Year (n = 17)	No DRT Within First Year (n = 1,071)	p Value
Baseline clinical characteristics			
Age, yrs	79.4 ± 7.1	75.1 ± 8.5	0.03
Male	64.7	64.5	1.00
AF at time of implant	76.5	59.2	0.21
Hypertension	82.4	83.9	0.75
Congestive heart failure	29.4	16.5	0.18
Previous stroke	35.3	27.4	0.43
Previous TIA	11.8	10.6	0.70
Previous major bleed	64.7	71.8	0.59
Previous PCI or CABG	17.6	25.6	0.58
Peripheral vascular disease*	5.9	15.5	0.50
CHA_2DS_2-VASc score	4.8 ± 1.9	4.2 ± 1.6	0.22
HAS-BLED score	3.1 ± 0.8	3.3 ± 1.1	0.49
Contraindication to OAC	82.4	82.8	1.00
Procedural characteristics			
LAA orifice width at widest point, mm	24.9 ± 4.4	22.3 ± 5.0	0.02
LAA landing zone width, mm	21.8 ± 3.5	20.5 ± 3.9	0.15
LAA depth, mm	29.5 ± 8.8	26.4 ± 8.2	0.16
TEE guided	88.2	88.0	1.00
ICE guided	11.8	12.0	
Device size			0.78
16 mm	0.0	3.0	
18 mm	0.0	5.1	
20 mm	0.0	10.7	
22 mm	29.4	21.5	
25 mm	52.9	35.7	
28 mm	11.8	15.0	
31 mm	5.9	6.9	
34 mm	0.0	2.2	
Discharge antithrombotic medications			
Single APT only	11.8	22.7	0.51
Dual APT only	58.8	57.6	
Anticoagulation (± APT)	29.4	17.5	
No antithrombotic therapy	0.0	2.2	

Values are mean ± SD or % of group. *Peripheral arterial or venous disease.

AF = atrial fibrillation; APT = antiplatelet therapy; CABG = coronary artery bypass grafting; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; DRT = device-related thrombus; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; ICE = intracardiac echocardiography; LAA = left atrial appendage; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

TABLE 2 Clinical Outcomes*

	DRT Within First Year (n = 17)	No DRT Within First Year (n = 1,071)	p Value
Ischemic stroke	3 in 3 patients	26 in 24 patients	
Annualized rate	18.3%	2.6%	<0.01
Compared with CHA_2DS_2-VASc (predicted rate)	136% increase (7.8% expected)	61% reduction (6.7% expected)	
≤7 days of implant	0	4	
>7 days of implant	3	22	
TIA	0	9 in 9 patients	
Annualized rate	0%	0.9%	
≤7 days of implant	0	0	
>7 days of implant	0	9	
Major bleed	1 in 1 patient	102 in 86 patients	
Annualized rate	6.1%	10.4%	0.60
≤7 days of implant	1	29	
>7 days of implant	0	73	
DRT	18 in 17 patients		
≤7 days of implant	1		
>7 days of implant	17		
All-cause mortality rate	14.4	8.3	0.64
CV cause	2	52	
Non-CV cause	0	34	
≤7 days of implant	0	3	
>7 days of implant	2	83	

*All events were adjudicated by a clinical events committee.
CV = cardiovascular; other abbreviations as in Table 1.

Fifty-two deaths in the non-DRT group were due to cardiovascular causes.

The Central Illustration shows Kaplan-Meier curves comparing clinical outcomes between groups. Five (29.4%) DRT patients and 77 (7.2%) non-DRT patients experienced a CV death, ischemic stroke, or TIA. Three (17.6%) DRT patients, and 32 (3.0%) non-DRT patients, suffered an ischemic stroke or TIA. After adjusting for baseline CHA_2DS_2-VASc and HAS-BLED scores, the presence of a DRT was associated with an increased risk for the composite endpoints of CV death, ischemic stroke, or TIA (HR: 4.10; 95% CI: 1.64 to 10.25; p = 0.003) and ischemic stroke or TIA (HR: 5.27; 95% CI: 1.58 to 17.55; p = 0.007).

Results of the univariate and multiple regressions for DRT formation are listed in Table 3. Age, AF status, history of congestive heart failure, CHA_2DS_2-VASc score, and LAA orifice width had p values <0.20 in univariable analysis and were included in the multiple regression analysis. LAA orifice width (HR: 1.09; 95% CI: 1.00 to 1.19; p = 0.04) was a significant predictor for DRT formation, while age was borderline significant (HR: 1.08; 95% CI: 0.99 to 1.16; p = 0.06).

TIMING OF DRT DETECTION AND FOCUSED ECHOCARDIOGRAPHIC ANALYSIS OF DRT PATIENTS. DRT was observed during standard follow-up TEE in 10 cases, unscheduled follow-up TEE in 7 cases, and CT in 1 patient. A TEE was acquired during 14 of the 29 hospitalizations for ischemic stroke. Procedural and follow-up echocardiographic analysis of DRT patients are shown in Table 4. Procedural echocardiograms were available for Amulet device positioning review in 11 DRT patients. Technical issues prevented procedural echocardiogram review in the remaining 6 DRT patients. The lobe position was deemed appropriate in 7 patients, too distal in 3, and too proximal in a single patient. The superior edge of the disc to the pulmonary vein (PV) ridge was 13 ± 5 mm (range 0 to 18 mm), with the distance being above 10 mm, or the disc completely within the LAA, in most cases (9 of 11), indicating suboptimal implantation. The device appeared undersized in 5 of 11 cases. Nevertheless, adequate LAAO (no peridevice leak of any size), as interpreted by the echocardiographic core laboratory, was present in 100% of DRT patients evaluated during the procedure and at 1 to 3 months. Similarly, adequate LAAO was observed in 99.3% and 98.3% of non-DRT patients at the procedure and 1 to 3 months, respectively.

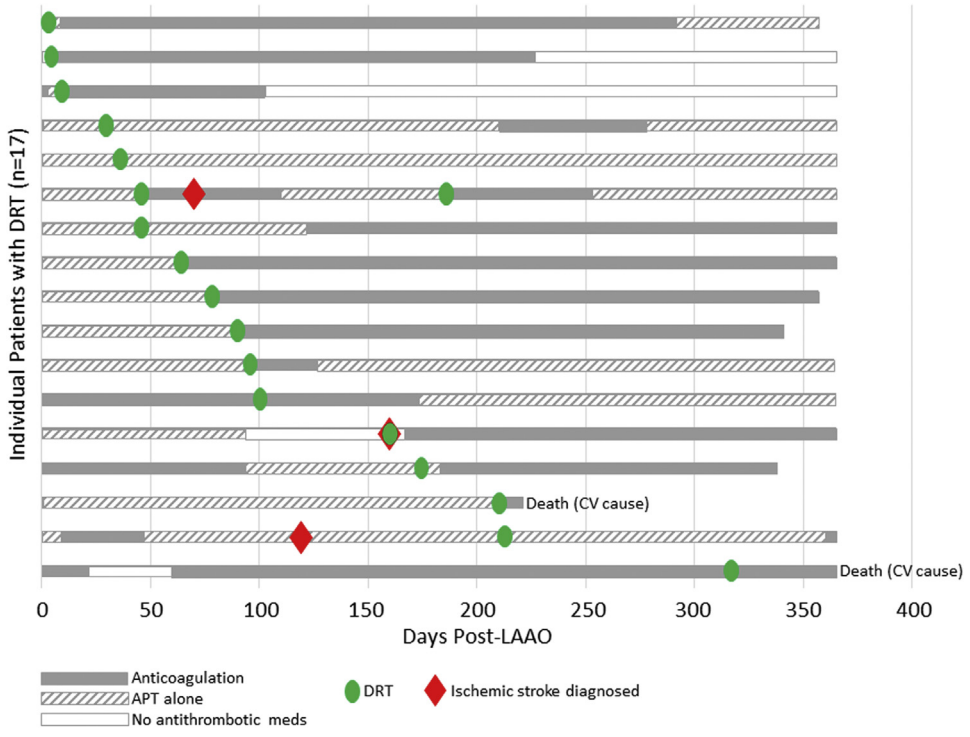
Fifteen post-procedural TEEs, from 10 patients, were available for detailed DRT characterization. Technical issues prevented post-procedural TEE review in 6 DRT patients, while 1 DRT was observed on a CT and not characterized. The primary DRT was mostly (87%) located at the upper edge of the disc near the PV ridge. The primary DRT was diffuse in 53% and mobile in 47% of cases. A secondary DRT was observed in 2 cases, located on the end screw in both instances. Figure 2 illustrates the types of thrombus observed.

DISCUSSION

The current prospective multicenter study consists of the largest collection of patients undergoing LAAO with the AMPLATZER Amulet device in a real-world observational setting. The main findings are: 1) in a population of patients primarily (80.1%) discharged on APT alone, DRT was infrequent, observed at a rate of 1.7% over the first year; 2) the presence of a DRT increases the risk of clinical events as compared with patients without DRT, although the majority (82.3%) of DRT patients did not experience a thromboembolic event; and 3) most DRTs developed near the superior edge of the Amulet disc close to the PV ridge, with an uncovered PV ridge as a potential contributing factor.

DRT INCIDENCE AND COMPARISON WITH PUBLISHED STUDIES. The 1.7% observed DRT rate in the current study is comparable to previous reports of AMPLATZER LAAO devices. In a prospective single-center study of 110 consecutive patients implanted

FIGURE 1 Timeline of DRT Observation



A **bar** represents the follow-up duration for each device-related thrombus (DRT) patient. The **bar shading** depicts the antithrombotic medication regimen over time. APT = antiplatelet therapy; CV = cardiovascular; LAAO = left atrial appendage occlusion.

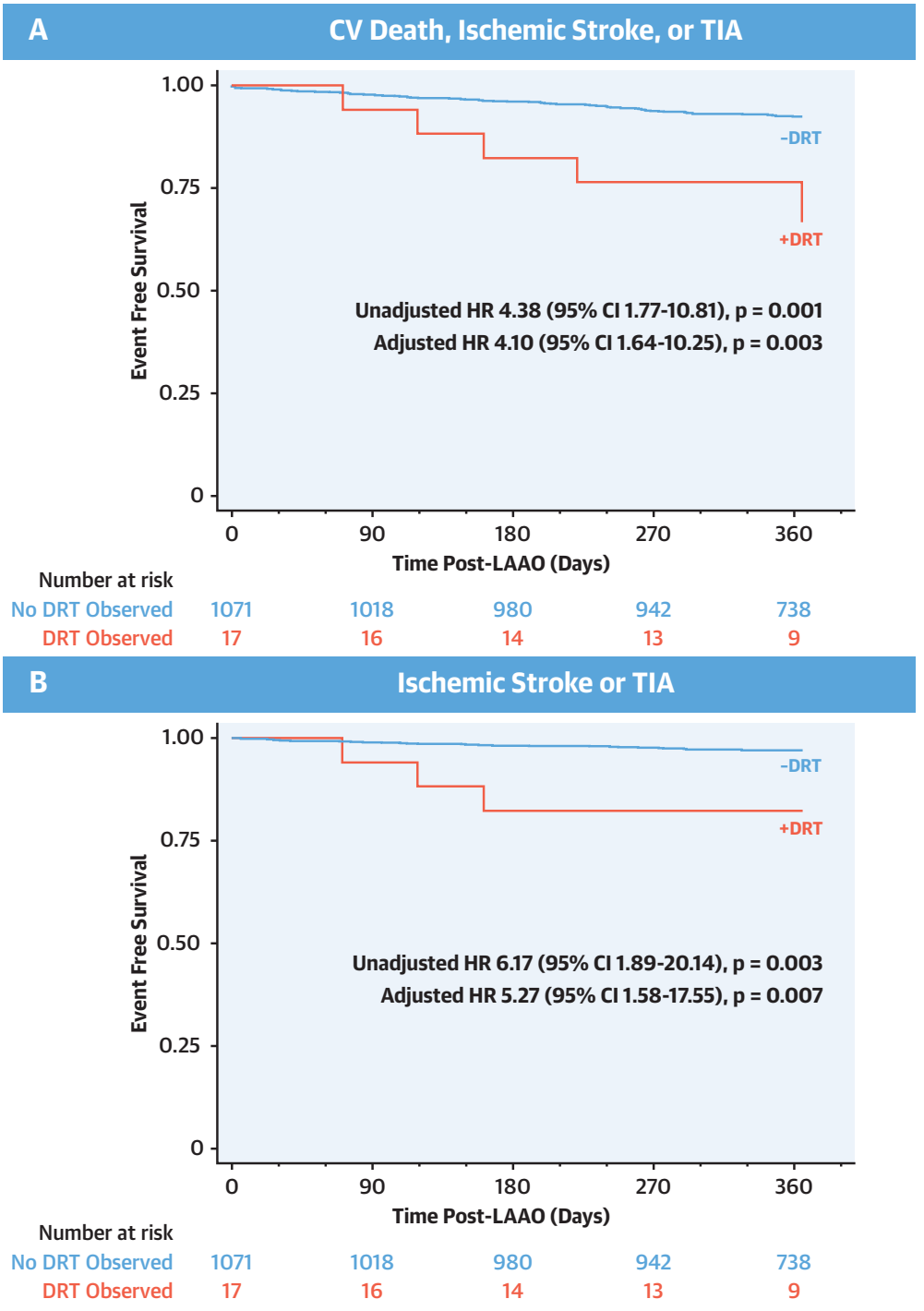
with AMPLATZER devices and treated with aspirin monotherapy, the DRT rate was 1.9% after a median follow-up of 2.3 years (2). Similar DRT rates were seen in 2 larger registries. Among 218 AMPLATZER devices with 6-month TEE follow-up in the Italian registry, DRT was present in 1.8% of patients (1). The Iberian registry, consisting of patients contraindicated to OAC, reported a DRT rate of 2.4% in 205 patients receiving an Amulet device (7).

In contrast to those 3 reports, 2 recent studies describe higher incidences of DRT following LAAO with an Amulet device. In a small series of 24 patients discharged on dual APT, Sedaghat et al. (13) observed DRT on TEE in 16.7% of patients after 11.0 ± 8.2 weeks. All DRTs were observed within the untrabeculated region of the LAA ostium between the PV ridge and the Amulet disc, indicative of suboptimal LAA occlusion.

A recently published French multicenter registry (3) enrolled 197 consecutive AMPLATZER device patients (100 AMPLATZER Cardiac Plug, 97 Amulet device), with patients often discharged on single (44.7%) or dual (23.4%) APT or no antithrombotic therapy (13.2%). Follow-up imaging was available in 51.3% of AMPLATZER device patients, with both TEE and CT utilized. DRT rates for AMPLATZER Cardiac Plug and Amulet devices were 8.2% and 25.0%, respectively. Unlike the study by Sedaghat et al. (13), the French registry did not detail procedural characteristics such as location of the disc relative to the PV ridge. The lack of follow-up imaging in a large proportion of patients, and use of multiple antithrombotic regimens, may represent clinical practice in the real world, but limits generalization of the results.

CLINICAL IMPACT OF DRT. There is currently no consensus if DRT are associated with adverse clinical events such as ischemic stroke, TIA, or CV death. Multiple studies evaluating WATCHMAN (4,18) and AMPLATZER (10,11,18) LAAO devices have reported no occurrence of events in patients with DRT, or at rates similar to those without DRT. However, more recent studies suggest a 3- to 4.5-times increased risk of thromboembolic events in patients with DRT. Dukkipati et al. (5) analyzed data from the 1,739 patients receiving a WATCHMAN device in the PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in

CENTRAL ILLUSTRATION **Kaplan-Meier Survival Curves for Cardiovascular Events in Patients With and Without DRT**



Aminian, A. et al. J Am Coll Cardiol Intv. 2019;12(11):1003–14.

(A) Device-related thrombus (DRT) was associated with higher rates of ischemic stroke, transient ischemic attack (TIA), and cardiovascular (CV) death. **(B)** The rates of ischemic stroke and TIA were also higher in DRT patients. Hazard ratios (HRs) were adjusted for CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category) and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) scores. CI = confidence interval; LAAO = left atrial appendage occlusion.

Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials and the 2 subsequent continuing access protocols. DRT was observed in 65 (3.74%) patients, with ischemic stroke or systemic embolism occurring in 25.0% of DRT patients compared with 6.8% of patients without DRT. After adjusting for baseline CHA_2DS_2-VASc and HAS-BLED scores, the HR for ischemic stroke or systemic embolism was 3.22 based on the presence of a DRT. Relative to stroke or systemic embolism, DRT observation within 1 month implied temporal causality in 47.4% of events, and 63.2% of events if a 6-month window was utilized. Importantly, despite the suggestion of a causative relationship, the majority (86.6%) of strokes and systemic embolisms occurred in patients without DRT. In 2 additional studies following patients implanted with WATCHMAN, AMPLATZER Cardiac Plug, or Amulet devices, patients with DRT had stroke incidence rates of 15% (3) and 11.1% (7) compared with 3.2% (3) and 2.6% (7) for patients without DRT.

The present study supports the recent change in perception that DRT may be associated with deleterious clinical events. The annualized rate of ischemic stroke was 7 times greater in patients with DRT, as compared with those without DRT (18.3%/year vs. 2.6%/year). After adjusting for baseline CHA_2DS_2-VASc and HAS-BLED scores, the hazard ratio for ischemic stroke or TIA was 5.3 based on the presence of a DRT. Furthermore, 29.4% of DRT patients had an ischemic stroke, TIA, or death adjudicated as cardiovascular in nature, while only 7.2% of non-DRT patients experienced the same outcomes. Although the presence of DRT was confirmed at the time of stroke in only 1 of 3 DRT patients, a time window of 3 months between DRT diagnosis and ischemic stroke was used to define causality. As such, the occurrence of an ischemic stroke 24 days after DRT diagnosis in a patient receiving dabigatran, and DRT diagnosis 91 days following ischemic stroke in a patient maintained on aspirin monotherapy, are likely related. DRT presents a difficult patient management scenario, as 83% of enrolled patients were contraindicated to OAC and 72% had a history of major bleeding (14). Fortunately, no major bleeds occurred in patients following DRT, as 83% received anticoagulants to resolve the thrombus.

PREDICTORS OF DRT WITH THE AMULET OCCLUDER. Despite the relatively small number of DRTs observed in the current study, we found an increased risk of DRT formation with an increase in LAA orifice width. Dukkipati et al. (5) recently reported similar results in WATCHMAN patients, suggesting that suboptimal LAAO may occur more frequently in larger LAAs. Our focused analysis of

TABLE 3 Univariate and Multiple Regression Analysis of Device-Related Thrombus

	Univariable Analysis		Multiple Regression Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.08 (1.01–1.16)	0.03	1.08 (0.99–1.16)	0.06
Male	1.02 (0.38–2.77)	0.96		
AF at time of implant	2.33 (0.76–7.13)	0.14	1.80 (0.58–5.56)	0.31
Hypertension	0.91 (0.26–3.17)	0.88		
Congestive heart failure	2.15 (0.76–6.09)	0.15	1.94 (0.62–6.06)	0.25
Previous stroke	1.41 (0.52–3.81)	0.50		
Previous TIA	1.16 (0.26–5.05)	0.85		
Previous major bleed event	0.71 (0.26–1.93)	0.51		
Previous PCI or CABG	0.63 (0.18–2.20)	0.47		
Peripheral vascular disease	0.36 (0.05–2.68)	0.32		
CHA_2DS_2-VASc score	1.30 (0.97–1.75)	0.08	1.10 (0.78–1.55)	0.60
HAS-BLED score	0.85 (0.55–1.33)	0.49		
Contraindication to OAC	0.99 (0.29–3.45)	0.99		
LAA orifice width	1.10 (1.01–1.19)	0.03	1.09 (1.00–1.19)	0.04
Discharged on anticoagulation (OAC or LMWH, ± APT) vs. APT alone	1.91 (0.67–5.43)	0.22		

CI = confidence interval; HR = hazard ratio; LMWH = low-molecular-weight heparin; other abbreviations as in Table 1.

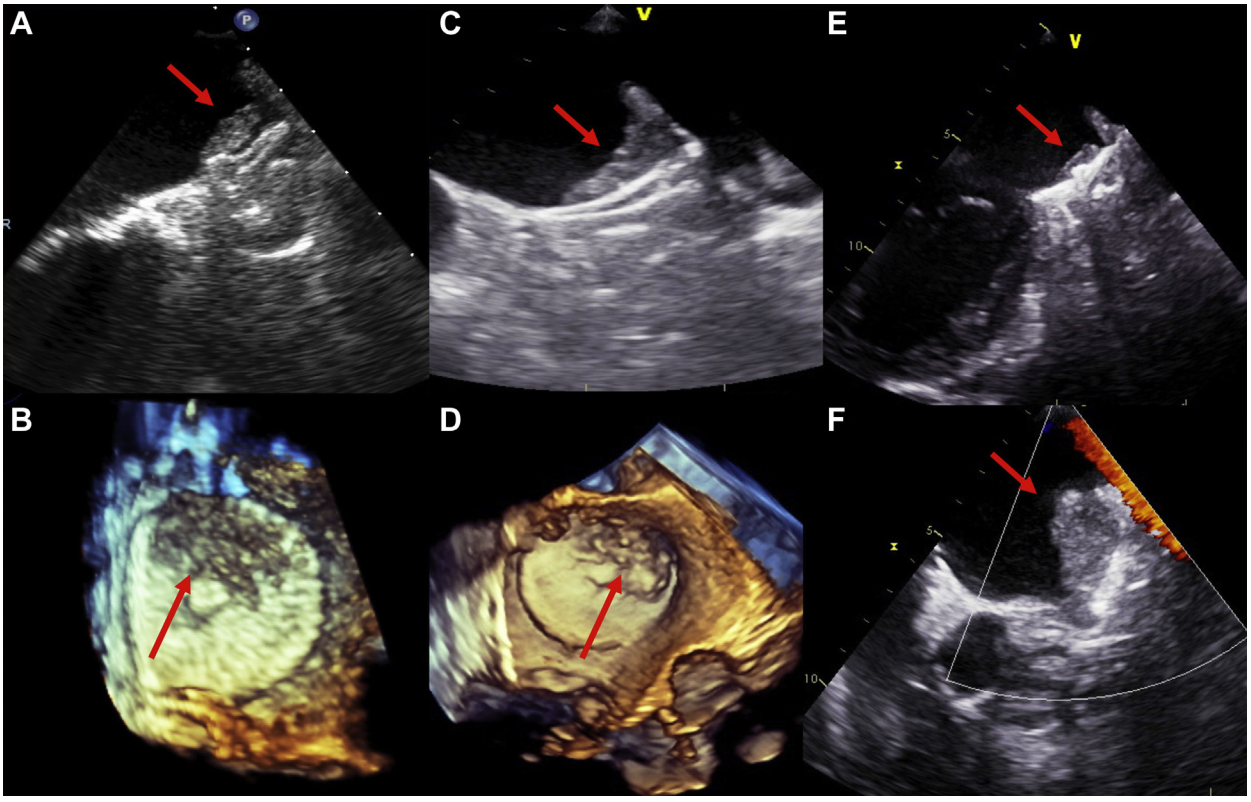
TABLE 4 Focused Echocardiographic Analysis in Patients With DRT

	Patients With DRT Within the First Year
Procedural	
Lobe position	
Appropriate	7/11 (64)
Too distal	3/11 (27)
Too proximal	1/11 (9)
Lobe off-axis	2/10 (20)*
Device undersized	5/11 (45)
Distance from superior edge of disc to PV ridge, mm	13 ± 5
Distance from superior edge of disc to PV ridge >10 mm	9/11 (82)
Follow-up	
Primary DRT located at superior edge of the disc	13/15 (87)
Primary DRT diffuse	8/15 (53)
Primary DRT mobile	7/15 (47)
Primary DRT laminar (vs. pedunculated)	11/15 (73)
Primary DRT irregular (vs. smooth)	10/15 (67)
Secondary DRT	2/15 (13)
Presence of spontaneous echo contrast	10/15 (67)

Values are n/N (%) or mean ± SD. Procedural echocardiograms were available for review in 11 patients; 15 follow-up echocardiograms, from 10 patients, allowed for DRT characterization. *Poor image quality prevented lobe axis assessment in 1 study.

DRT = device-related thrombus; PV = pulmonary vein.

FIGURE 2 Characterization of DRT on Amulet Device



The most common location of device-related thrombus (DRT) formation was the upper aspect of the disc, close to an uncovered pulmonary vein ridge, as depicted in **(A)** 2-dimensional and **(B)** 3-dimensional transesophageal echocardiography (TEE) images from the same patient. **(C and D)** A similar DRT was observed on a disc positioned within the orifice of the left atrial appendage. DRTs were observed **(E)** less commonly around the central pin and **(F)** covering the entire disc in a diffuse manner. **Red arrows** indicate location of DRT.

implant procedures found the Amulet device to be undersized in nearly one-half the cases of DRT patients. Appropriate device sizing may be improved by using pre-procedural CT. LAA orifice and landing zone widths have been reported to be smaller on TEE than on CT, with CT considered to be the gold-standard for LAA characterization (19,20).

Although less clinically relevant for patient selection, our finding of DRT formation being associated with increasing age was previously reported in a study (3) involving both WATCHMAN and AMPLATZER devices. Predictors of DRT formation in the current study were evaluated based upon a single device and relatively homogenous post-LAAO antithrombotic medication regimen (predominately APT alone). Thus, generalization to other devices should be made with caution. Furthermore, DRTs occurring in only 17 patients may have limited our ability to identify physiologically plausible predictors of DRT formation, including AF status, history of stroke, and decreased ejection fraction as reported in studies with higher DRT incidence rates (3,5).

Our small sample of DRT patients tended to be discharged on anticoagulants more often than non-DRT patients. Some studies report no association between medication regimen and DRT formation (4), while others suggest a link (3). Future investigations, such as the currently enrolling ANDES (Short-term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Transcatheter Left Atrial Appendage Closure) trial (NCT03568890) randomizing patients to direct oral anticoagulants or DAPT for 8 weeks following LAAO, should evaluate whether discharge medication regimen is related to DRT formation.

DEVICE IMPLANTATION FEATURES AND THROMBUS CHARACTERIZATION IN DRT PATIENTS. In nearly

all implants of patients later presenting with DRT, the PV ridge was not covered by the disc, supporting an observation made in 2 prior studies (13,21). Moreover, the vast majority of thrombus (87%) were found to be located in the untrabeculated area of the LAA ostium between the PV ridge and the upper edge of the Amulet disc. Although not all anatomies allow for adequate coverage of the PV ridge, the device was determined to be undersized in almost one-half of DRT patients. Despite procedural and 1- to 3-month follow-up TEE studies not showing peridevice flow in any DRT patients, incomplete LAAO and subsequent peridevice leaks may be underappreciated on TEE, as compared with more sensitive CT (18,22). Turbulent blood flow near a cul-de-sac formed by the disc edge and the PV ridge, often combined with the presence of spontaneous echo contrast due to reduced LA blood flow velocity, may result in an environment promoting thrombogenicity (13). Future studies should assess whether optimization of device implantation could represent an important future target for the prevention of DRT.

STUDY LIMITATIONS. The echo core laboratory only reviewed 95.2% of TEEs acquired 1 to 3 months post-LAAO or at unscheduled timepoints. Site-reported information for DRT diagnosis, and the echo core laboratory not reviewing 4.8% of TEEs, may have resulted in under-reporting of the DRT incidence. Echocardiographic characterization of the Amulet device positioning at procedure was not performed on patients without DRT observed over the first year and was only able to be performed on 11 of 17 DRT patients. There may be other implant characteristics associated with DRT formation that were not assessed. This limits our assessment of implant characteristics and their impact on DRT formation. Furthermore, the results of this study may not be applicable to other LAAO devices. The relatively few patients experiencing a DRT limit our ability to evaluate if some DRT characteristics are associated with ischemic stroke or TIA. Finally, not all patients received a TEE to evaluate for presence of DRT at the time of ischemic stroke or TIA, despite the protocol requirement. Although this may have led to under-reporting of the DRT rate, the practice reflects the standard of care observed in this study.

CONCLUSIONS

In a large prospective multicenter cohort of AF patients undergoing LAAO with an AMPLATZER Amulet device, mainly discharged on APT alone, DRT was observed at a low rate of 1.7%/year. Incomplete coverage of the PV ridge by the Amulet disc was frequently documented in patients with DRT, indicating suboptimal implantation. Although most patients with DRT did not experience an ischemic stroke, the presence of DRT was associated with an increased rate of ischemic stroke and CV mortality, suggesting the importance of close clinical monitoring in case of DRT diagnosis.

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PERSPECTIVES

WHAT IS KNOWN? DRT is a potential complication following LAAO. The incidence, predictors, and clinical impact of DRT formation are not well defined and can vary by LAAO device.

WHAT IS NEW? Results from this large multicenter global observational experience suggest that the incidence of DRT following LAAO with the AMPLATZER Amulet device is low but associated with an increased risk of CV events. Suboptimal implantation characteristics were commonly observed in patients with DRT.

WHAT IS NEXT? Future studies are needed to define appropriate strategies to prevent DRT. Among these, the impact of optimized device implantation should be further assessed.

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KEY WORDS atrial fibrillation, LAA occlusion, stroke, thrombus

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