

Device-Related Thrombosis After Percutaneous Left Atrial Appendage Occlusion for Atrial Fibrillation



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ABSTRACT

BACKGROUND Transcatheter left atrial appendage (LAA) occlusion is an alternative strategy for stroke prevention in patients with atrial fibrillation (AF).

OBJECTIVES This study sought to determine the incidence, predictors, and prognosis of thrombus formation on devices in patients with AF who were treated with LAA closure.

METHODS The study retrospectively analyzed data from patients treated with 2 LAA closure devices seen in 8 centers in France from February 2012 to January 2017.

RESULTS A total of 469 consecutive patients with AF underwent LAA closure (272 Watchman devices [Atritech, Boston Scientific, Natick, Massachusetts] and 197 Amplatzer devices [St. Jude Medical, Minneapolis, Minnesota]). Mean follow-up was 13 ± 13 months, during which 339 (72.3%) patients underwent LAA imaging at least once. There were 98 major adverse events (26 thrombi on devices, 19 ischemic strokes, 2 transient ischemic attacks, 18 major hemorrhages, 33 deaths) recorded in 89 patients. The incidence of device-related thrombus in patients with LAA imaging was 7.2% per year. Older age (hazard ratio [HR]: 1.07 per 1-year increase; 95% confidence interval [CI]: 1.01 to 1.14; p = 0.02) and history of stroke (HR: 3.68; 95% CI: 1.17 to 11.62; p = 0.03) were predictors of thrombus formation on the devices, whereas dual antiplatelet therapy (HR: 0.10; 95% CI: 0.01 to 0.76; p = 0.03) and oral anticoagulation at discharge (HR: 0.26; 95% CI: 0.09 to 0.77; p = 0.02) were protective factors. Thrombus on the device (HR: 4.39; 95% CI: 1.05 to 18.43; p = 0.04) and vascular disease (HR: 5.03; 95% CI: 1.39 to 18.23; p = 0.01) were independent predictors of ischemic strokes and transient ischemic attacks during follow-up.

CONCLUSIONS Thrombus formation on the device is not uncommon in patients with AF who are treated by LAA closure. Such events are strongly associated with a higher risk of ischemic stroke during follow-up. (REGistry on Real-Life EXperience With Left Atrial Appendage Occlusion [RELEXAO]; [NCT03279406](https://clinicaltrials.gov/ct2/show/study/NCT03279406)) (J Am Coll Cardiol 2018;71:1528-36)
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Percutaneous left atrial appendage (LAA) occlusion is an alternative to lifelong oral anticoagulation (OAC) for stroke prevention in patients with nonvalvular atrial fibrillation (AF) and with contraindications to OAC (1). The 2 most commonly used LAA closure systems are the Watchman nitinol cage device (Atritech, Boston Scientific, Natick, Massachusetts) and the Amplatzer LAA occluder device (St. Jude Medical, Minneapolis, Minnesota), which consists of a nitinol cylinder connected to a disk to form a nitinol plug. The main evidence supporting the non-inferiority of LAA occlusion versus warfarin comes from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) (2,3) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) (4) randomized trials using the nitinol cage device. The safety and feasibility of its use were assessed in the CAP (Continued Access to PROTECT AF) (5) and EWOLUTION (Registry on WATCHMAN Outcomes in Real-Life Utilization; NCT01972282) registries (6). Data from large observational studies also support the safety, efficacy, and feasibility of LAA occlusion with the nitinol plug device (7-11).

SEE PAGE 1537

Thrombus formation on the device is a possible finding during follow-up after LAA closure. Most studies report an incidence of device-associated thrombus close to 3% to 6%, although a higher rate was reported in a small study (12). The clinical significance of thrombus formation on the device is poorly known, and whether it is associated with more frequent occurrence of ischemic strokes is debated (10,13,14). Moreover, consensus on appropriate antithrombotic regimens after LAA closure remains an issue. The aim of this study was to evaluate, in daily practice, clinical outcomes in patients using the 2 main LAA closure systems, differences in antithrombotic management at discharge from hospital, and the incidence, predictors, and prognosis of thrombus formation on the device after LAA occlusion.

METHODS

STUDY DESIGN AND STUDY GROUP. In this retrospective cohort study, we centralized and analyzed

data from all patients with AF who were treated with LAA closure in 8 French cardiology departments from February 2012 to January 2017. These centers acquired their data prospectively and then agreed to contribute to this pooled analysis. Subjects eligible for LAA closure, according to appropriate local and European guidelines (1,15), were recruited from the general population in each institution, with a multidisciplinary decision taken in all centers. All physicians who performed device insertion procedures attended a thorough training and certification program to ensure an appropriate level of expertise and to minimize risk to patients.

STUDY ASSESSMENTS AND OUTCOMES. Patient follow-up was conducted according to each institution's standard practice, and antithrombotic management was decided for each patient on an individual basis. A clinical visit between 1 and 3 months post-procedure and follow-up visits at 6, 12, and 24 months were generally performed. LAA imaging to detect thrombus on the device and peridevice leaks was performed by 2-dimensional transesophageal echocardiography (TEE) or a computed tomography (CT) scan done between 1 and 3 months after LAA closure, and then generally at 12 months, following a consensus proposed by the French Society of Cardiology (15). A committee of 3 investigators (B.P., P.D., J.C.D.) evaluated all TEE and CT scans in which a thrombus was identified, and consensus for diagnosis was obtained in case of disagreement.

Reporting on adverse events in this study used as its basis the monitoring that was done until the end of the follow-up period. Death, cardiovascular death, ischemic stroke, and transient ischemic attack (TIA) definitions were established according to Valve Academic Research Consortium criteria (16). A Bleeding Academic Research Consortium type 3 or more hemorrhage was considered a major hemorrhage (17). A device-related thrombus was defined as the detection of a thrombus adherent to the luminal (left atrial) side of the device by TEE or CT scan. Major adverse events were defined as all-cause death, ischemic strokes or TIAs, major hemorrhages, and device-related thrombus occurring during follow-up.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CT = computed tomography
DAPT = dual antiplatelet therapy
LAA = left atrial appendage
OAC = oral anticoagulation
TEE = transesophageal echocardiography
TIA = transient ischemic attack

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TABLE 1 Baseline Characteristics of Patients Treated With LAA Occlusion

	All Patients (N = 487)	Nitinol Cage (n = 272)	Nitinol Plug (n = 197)	p Value (Nitinol Cage vs. Nitinol Plug)
Age, yrs	74.9 ± 8.9	74.6 ± 9.2	75.6 ± 8.5	0.25
Men	299 (61.4)	169 (62.1)	112 (61.9)	0.99
Medical history				
Hypertension	328 (84.1)	217 (84.1)	102 (85.7)	0.69
Diabetes mellitus	119 (30.6)	76 (29.6)	39 (32.8)	0.53
Ischemic stroke	179 (41.1)	102 (38.6)	69 (44.2)	0.26
Vascular disease	141 (43.4)	85 (44.0)	50 (42.0)	0.73
Permanent AF	244 (51.2)	132 (49.6)	102 (52.0)	0.61
LV ejection fraction, %	55.9 ± 10.0	56.4 ± 9.3	55.4 ± 10.4	0.32
LAA maximum diameter, mm (n = 353)	21.9 ± 4.4	21.4 ± 4.1	22.6 ± 4.9	0.01
CHA ₂ DS ₂ -VASc score	4.5 ± 1.4	4.4 ± 1.5	4.7 ± 1.2	0.008
HAS-BLED score	3.7 ± 1.0	3.7 ± 1.0	3.8 ± 1.0	0.08
Indication				
Previous bleeding	426 (90.1)	237 (89.4)	174 (91.1)	0.55
Contraindication to OAC	345 (72.8)	199 (74.8)	136 (71.2)	0.40
Recurrent ischemic stroke	25 (5.3)	18 (6.8)	5 (2.6)	0.05
LAA closure device				
Nitinol cage	272 (55.9)	—	—	—
Nitinol plug	197 (40.5)	—	—	—
WaveCrest	2 (0.4)	—	—	—
Implantation failure	16 (3.3)	—	—	—
Antithrombotic therapy at discharge				
No OAC, no APT	37 (7.7)	9 (3.3)	26 (13.2)	<0.0001
Single APT	171 (35.8)	82 (30.1)	88 (44.7)	0.002
Dual APT	110 (23.0)	63 (23.2)	46 (23.4)	0.96
OAC, no APT	138 (28.9)	101 (37.1)	34 (17.3)	<0.0001
OAC plus APT	22 (4.6)	17 (6.3)	3 (1.5)	0.009
LAA imaging during follow-up*	340 (72.1)	238 (87.5)	101 (51.3)	<0.0001

Values are mean ± SD or n (%). Percentages calculated from available data. *In patients with implanted device.
AF = atrial fibrillation; APT = antiplatelet therapy; CHA₂DS₂-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, and female sex; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly (age <65 years), drug or alcohol use; LAA = left atrial appendage; LV = left ventricular; OAC = oral anticoagulation.

No industry support was provided for this study. Industry had no role in the design, conduct, data analysis, or manuscript writing of the study. The study was approved by the Institutional Review Board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 12, 2015 and was considered a clinical audit; ethical review was not therefore required. Patients' consent was not sought. Patients' data were used only to facilitate the cross-referencing of data sources, and records were otherwise kept anonymous. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. The study has been registered on Clinicaltrials.gov (NCT03279406).

STATISTICAL ANALYSIS. Statistical analysis was performed using Statview version 5.0 software (SAS

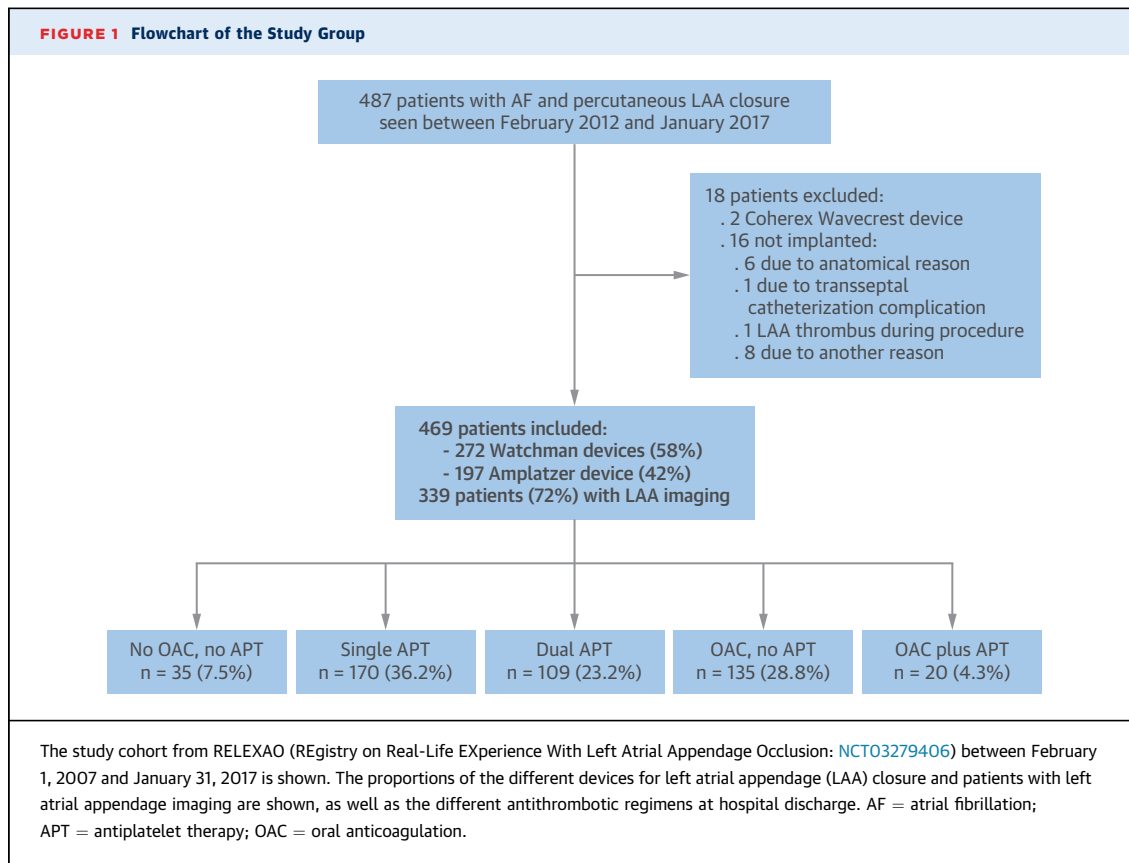
Institute, Inc., Cary, North Carolina). Comparisons between groups were made using the Student's *t*-test, or the nonparametric Mann-Whitney *U* test when appropriate, for continuous variables and the chi-square test for categorical variables. A Cox regression model was used for multivariable analysis. A *p* value of 0.25 was used as the cutoff to select univariate variables for inclusion in the multivariable analysis. A 2-sided *p* value <0.05 was then considered statistically significant.

RESULTS

STUDY GROUP. A total of 487 consecutive patients with AF underwent LAA closure from February 2012 to January 2017 in 8 French centers. The characteristics of these patients are detailed in Table 1. The rate of successful device implantation was 96.7%. Overall, 272 patients underwent device insertion with a nitinol cage device (58.0%) and 197 with an Amplatzer device (42.0%, including 100 patients with the Amplatzer Cardiac Plug and 97 with the newer version of this device, the Amplatzer Amulet). Two patients underwent successful LAA closure using a Coherex WaveCrest (Salt Lake City, Utah) device (0.4%). Of the 487 consecutive patients, the study group comprised 469 with LAA occlusion using the nitinol cage or nitinol plug devices (Figure 1).

STUDY TREATMENTS. Antithrombotic treatment at discharge is detailed in Table 1. Among patients treated with OAC, 43 of 155 (27.7%) were treated with non-vitamin K antagonist OAC. Compared with patients treated with the nitinol cage device, patients with the nitinol plug device had a higher mean CHA₂DS₂-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, and female sex) score, were less likely to be treated with OAC or antiplatelet therapy at discharge, and were less likely to undergo LAA imaging during follow-up. Among patients with a nitinol plug device, those with the newer version had a similar CHA₂DS₂-VASc score, but they were less likely to be treated with OAC at discharge and were less likely to undergo LAA imaging during follow-up.

OUTCOMES. Mean follow-up was 13 ± 13 months, during which 339 (72.3%) patients underwent LAA imaging at least once to detect thrombus on the device using TEE (n = 263) or a CT scan (n = 76). There were 98 major adverse events (26 thrombi on device, 19 ischemic strokes, 2 TIAs, 18 major hemorrhages, 33 deaths) recorded in 89 patients (Table 2). No intracranial bleeding was documented after device



implantation. Mean time to first LAA imaging was 2.8 ± 2.5 months, and mean time to thrombus detection on the device was 3.1 ± 2.6 months. The rate of thrombus on the device was 8.3% in patients with LAA imaging using TEE and 5.3% with LAA imaging using a CT scan ($p = 0.52$).

The overall incidence of thrombus on the device was 5.5% in patients treated with a nitinol cage device, 8.2% with the older version of the nitinol plug, and 25.0% with the newer version (overall $p = 0.001$). One patient had a stroke leading to atrial imaging and a diagnosis of thrombus on the LAA occluder device. There were 11 of 26 patients (42%) with thrombus detected within 7 weeks post-implantation. At the time of thrombus diagnosis, 11 of 26 patients (42%) were treated with single antiplatelet therapy, 1 of 26 (4%) was treated with dual antiplatelet therapy (DAPT), 9 of 26 (35%) were treated with OAC, and treatment was unknown in 1 patient of 26 (4%) who was treated with OAC at discharge. Patients with thrombus formation on the device were less likely to be treated with DAPT or antithrombotic therapy at discharge after LAA closure (Table 3).

On multivariable analysis, older age and history of stroke were predictors of thrombus formation on the

device, whereas DAPT and OAC at discharge were associated with a lower risk of thrombus on device (Table 4).

Information on subsequent antithrombotic therapy was available for 77% of patients with thrombus on the device: 30% had a change in therapy, mainly consisting of OAC initiation in those not previously treated with OAC. In patients with thrombus on the device, 4 of 26 had a stroke (1 of 26 had thrombus diagnosed at the time of stroke) and 1 of 26 died during follow-up compared with 10 of 313 and 20 of 313, respectively, in patients with no thrombus on LAA imaging. On multivariable analysis, only thrombus on the device and vascular disease were independent predictors of ischemic strokes and TIAs during follow-up (Table 4, Central Illustration).

DISCUSSION

We report the outcomes in a relatively large, multi-center, retrospective study of consecutive patients with AF who were treated with LAA closure, not restricted by the use of a single device. In this large analysis, industry had no role in the design, analysis, or reporting of the study. We found that the initial

TABLE 2 Major Adverse Events (n = 98) in Patients Treated With LAA Occlusion Using the Nitinol Plug or Nitinol Cage Devices

	Overall (N = 469)	Nitinol Cage (n = 272)	Nitinol Plug (n = 197)	p Value (Nitinol Cage vs. Nitinol Plug)
Death	33 (6.9)	18 (6.7)	15 (7.1)	0.85
Ischemic stroke	19 (4.0)	10 (3.7)	9 (4.3)	0.86
TIA	2 (0.4)	2 (0.7)	0 (0)	—
Major hemorrhage	18 (3.8)	10 (3.7)	8 (3.8)	0.76
Thrombus on the device				
In the whole study group	26 (5.4)	13 (4.8)	13 (6.2)	0.36
In patients with LAA imaging	26 (7.2)	13 (5.5)	13 (11.0)	0.02

Values are n (yearly rate %).
LAA = left atrial appendage; TIA = transient ischemic attack.

yearly rate of thrombus formation on devices was 7.2% in the group with LAA imaging during follow-up. Older age and history of stroke were risk factors for device-related thrombus, whereas DAPT and OAC at discharge were associated with a lower risk of thrombus formation. The presence of thrombus on the device and history of vascular disease were the only predictors of ischemic strokes or TIA during follow-up.

The antithrombotic regimen at discharge differed between the patients treated with the 2 devices, a

TABLE 3 Device-Related Thrombus Characteristics*

	Thrombus (n = 26)	No Thrombus (n = 313)	p Value
Age, yrs	76.1 ± 8.9	74.2 ± 9.0	0.31
Men	16 (61.5)	185 (59.1)	0.81
Medical history			
Hypertension	19 (79.2)	259 (86.3)	0.33
Diabetes mellitus	6 (25.0)	88 (29.4)	0.65
Ischemic stroke	14 (58.3)	129 (41.9)	0.12
Permanent AF	11 (42.3)	155 (49.7)	0.47
Previous bleeding	23 (92.0)	276 (90.2)	0.77
CHA ₂ DS ₂ -VASc score	4.7 ± 1.7	4.5 ± 1.4	0.49
HAS-BLED score	3.5 ± 1.3	3.7 ± 1.0	0.26
LV ejection fraction, %	53.1 ± 12.2	56.7 ± 9.4	0.15
LAA maximum diameter, mm (n=353)	22.2 ± 4.9	21.4 ± 4.3	0.48
Nitinol plug device	13 (12.9)	88 (87.1)	0.02
Nitinol cage device	13 (5.5)	225 (94.5)	0.02
Antithrombotic therapy at discharge			
No OAC, no APT	4 (15.4)	14 (4.5)	0.02
Single APT	11 (42.3)	91 (29.1)	0.15
Dual APT	1 (3.8)	81 (25.9)	0.01
OAC, no APT	10 (38.5)	108 (34.5)	0.68
OAC plus APT	0 (0.0)	19 (6.1)	0.23
Leaks			
Peridevice leakage	1 (3.8)	50 (16.0)	0.10
Peridevice leakage >5 mm	0 (0.0)	17 (5.4)	0.22

Values are mean ± SD or n (%). *Analysis restricted to patients with LAA imaging during follow-up. Abbreviations as in Table 1.

finding that may reflect historical trials and reports with each device (2,8,10,18). We found no difference in clinical outcomes between the 2 occlusion devices, consistent with a previous registry that compared outcomes with nitinol cage and nitinol plug devices, in a far smaller number of patients (19). However, we report higher rates of mortality, ischemic strokes, and major hemorrhages than in other studies (2,4,19). This finding may be explained by the older age, higher thromboembolic risk, and higher bleeding profile in our very high-risk patients: approximately 40% had a prior stroke, a rate markedly higher than in the EWOLUTION registry (6), and 90% had a prior bleeding episode. Our study reflects results obtained in a “real-life” practice for all patients treated with LAA occlusion at a nationwide level, who overall may be sicker than those patients included in a randomized trial (with no contraindication to OAC) or in other declarative registries. Underdiagnosis of events in other studies is also possible.

A recent systematic review reported a mean incidence of 3.4% for device-associated thrombus after LAA occlusion (13), whereas we found a higher overall rate. We found no significant difference in rates of thrombus when using TEE or CT scans for LAA imaging. The incidence of thrombus formation on devices varies widely in current registries (12,20), and this may be explained by the different sample sizes, lack of consensus on the definition of device-associated thrombus, or reporting bias related to different imaging methods and their frequency during follow-up. The 7.2% rate of device-related thrombus in our study is still within this range and is similar to rates in other large registries, although it is more likely to reflect the true incidence of thrombus on the device. Our result for thrombus incidence rate with the nitinol cage device (5.5%) is relatively consistent with rates observed in the PROTECT AF (2) and ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) studies (18), which were 4.2% and 4%, respectively. We found a higher rate of thrombus formation with a cardiac plug device, but the higher risk did not reach significance in multivariable analysis. We report an 11.0% rate of thrombus related to the nitinol plug devices in the first year, a rate that is higher than the 2% to 4% reported in other studies (10,21,22). The incidence of device-related thrombus with nitinol plug devices thus varies in published reports and may be higher when considering other registries (20).

The rate of device-related thrombus in our study may have been underestimated, considering the number of patients who did not undergo LAA imaging

TABLE 4 Multivariable Analysis (Cox Regression Model) for Predictors of Thrombus Formation on the Device and Predictors of Stroke and TIA*

	HR (95% CI)	p Value
Thrombus formation on the device		
Age (per 1-yr increase)	1.07 (1.01-1.14)	0.02
Previous ischemic stroke	3.68 (1.17-11.62)	0.03
CHA ₂ DS ₂ -VASc score	0.69 (0.44-1.06)	0.09
APT at discharge	0.35 (0.12-1.04)	0.06
Dual APT at discharge	0.10 (0.01-0.76)	0.03
OAC at discharge	0.26 (0.09-0.77)	0.02
Strokes or TIAs		
Vascular disease	5.03 (1.39-18.23)	0.01
Thrombus on the device	4.39 (1.05-18.43)	0.04
CHA ₂ DS ₂ -VASc score	0.71 (0.47-1.06)	0.09
APT at discharge	1.35 (0.20-9.06)	0.75
Dual APT at discharge	0.64 (0.15-2.69)	0.54
OAC at discharge	0.39 (0.06-2.61)	0.33

*Analysis restricted to patients with LAA imaging during follow-up. For prediction of thrombus formation on the device, time zero is time at discharge after LAA closure. For prediction of stroke or TIA, time zero is time at first post-procedure LAA imaging.
 CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

during follow-up. This suboptimal rate of imaging in daily practice (72% of patients) is a new finding and may be explained by the overall frailty of these high-risk patients. Many physicians also consider that imaging results are unlikely to change the antithrombotic strategy, while bearing in mind the debated clinical significance of device-related thrombus and the contraindication to OAC in many patients. A first message from our study could be that a wider use of LAA imaging may be promoted, considering the worse prognosis associated with device-related thrombus and the likely need to re-evaluate the antithrombotic strategy in patients with such a finding.

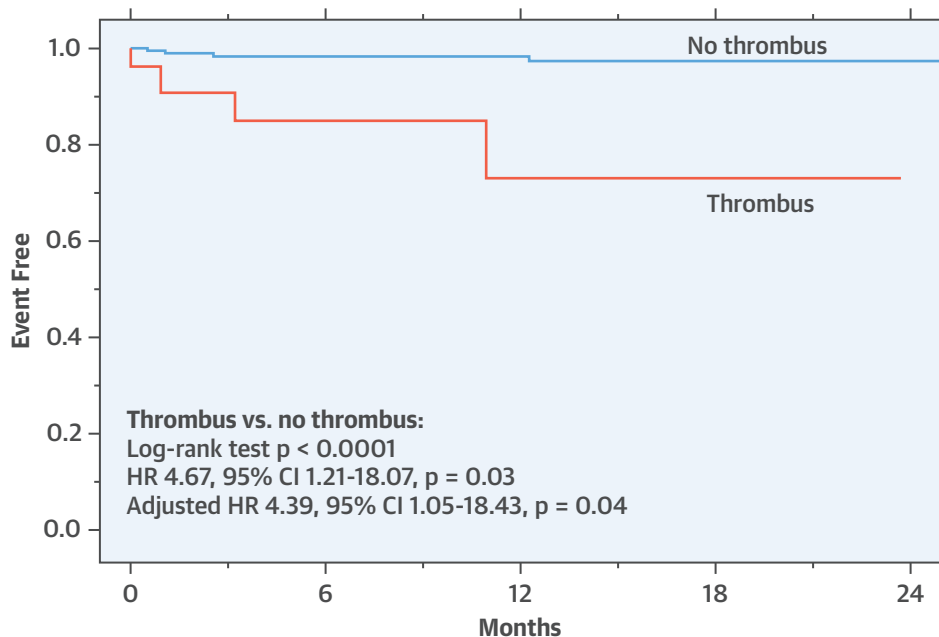
Limited data are available on risk factors for thrombus formation on the device (13,14). We found that older age and prior ischemic stroke were predictive of thrombus on the device. DAPT and OAC at discharge were associated with a lower risk of thrombus formation, and this finding may have clinical implications over longer-term follow-up. CHA₂DS₂-VASc score was not associated with more thrombus formation on device in this high-risk group of patients. Left ventricular ejection fraction in patients with thrombus developing on the device was often preserved in our study and was not significantly lower than in patients without device-related thrombus. The maximum diameter of the LAA, likely related to atrial volume and device size, and the rate of peridevice leaks were also similar in patients with versus without thrombus on their devices.

The prognosis associated with thrombus formation on the device is poorly known. In a cohort of 339 patients undergoing nitinol plug implantation, it was suggested that device-associated thrombus may have a low thromboembolic risk (14). By contrast, stroke, peripheral embolism, or cardiac death occurred at a rate of 3.4 per 100 patient-year follow-up in 93 patients undergoing LAA closure with the nitinol cage device (23). Considering all types of devices, a 7.3% rate of ischemic stroke or TIA has been reported in patients with device-related thrombus (13). In our study, using the 2 devices most commonly used for LAA occlusion, we found a yearly rate of 4.0% for ischemic stroke, a little lower than what would be expected for this study group (24) but higher than that in other studies of LAA closure (2,4,6,10,14,18,19). Importantly, we report that thrombus on the device was an independent factor strongly associated with strokes and TIA during follow-up. Causality between device-related thrombus and strokes cannot be retrospectively proven, but a direct relationship is plausible. However, patients with LAA closure have the propensity for other sources of emboli, and vascular disease was unsurprisingly also independently associated with a higher risk of stroke during subsequent follow-up.

Care should be exercised in the interpretation of data on the post-implantation regimen and the risk for subsequent device-related thrombus, given that the post-implantation regimen was not randomized, as in all recent studies on antithrombotic management after LAA occlusion (21,25). However, we found that DAPT at discharge was associated with a lower risk of thrombus formation on the device. This result concurs with previously suggested adequacy and better effectiveness of DAPT over OAC therapy after LAA closure. In the ASAP study (18), patients with contraindications to OAC were treated with DAPT for 6 months, followed by aspirin alone, and a device-related thrombus rate of 4% was reported. This rate is similar to the 4.2% rate of nitinol cage-associated thrombus in the PROTECT AF trial, in which patients were treated with warfarin for 45 days, followed by DAPT for 6 months (2). In a single-center prospective cohort, DAPT administered for 6 weeks following LAA closure was associated with less frequent device-related thrombus (1.7%) compared with OAC at discharge (15.8%), regardless of the type of device (26). Although these results appear to favor DAPT at discharge after LAA occlusion, generalization cannot be firmly recommended. First, nitinol cage and nitinol plug devices may have different thrombogenicity profiles and endothelialization processes (27), and different antithrombotic management may

CENTRAL ILLUSTRATION Kaplan-Meier Cumulative Event-Free Curves of Ischemic Strokes and Transient Ischemic Attacks With and Without Thrombus on the Device

Ischemic Stroke / Transient Ischemic Attack



N at risk

	0	6	12	18	24
No thrombus	300	100	72	62	39
Thrombus	25	12	6	2	0

Fauchier, L. et al. *J Am Coll Cardiol.* 2018;71(14):1528-36.

The curves are representative of being event-free for ischemic strokes and transient ischemic attacks, with and without thrombus on the device, after left atrial appendage occlusion. Time zero is time at first post-procedure left atrial appendage imaging. The curves demonstrate a higher risk for ischemic strokes or transient ischemic attacks in the patients with a diagnosis of device-associated thrombus after left atrial appendage occlusion. The mean follow-up time was 13 ± 13 months. CI = confidence interval; HR = hazard ratio.

be required for these 2 devices. Second, the issue of clopidogrel nonresponders has to be taken into account: in patients developing thrombus on the device and treated by DAPT after LAA closure, Ketterer et al. (28) identified three-fourths as clopidogrel nonresponders, a finding suggesting that DAPT may not be appropriate for every patient undergoing LAA occlusion. Third, other studies have reported evidence against the adequacy of DAPT to prevent thrombus formation on devices for some patients: Plicht et al. (12) reported a high rate of thrombus on the device in a group of patients undergoing LAA occlusion with the Amplatzer cardiac plug and treated with DAPT at discharge, thus indicating that DAPT may not be sufficiently protective. Finally, a lower hemorrhagic risk with DAPT compared with OAC is uncertain, and

we also found that OAC at discharge was associated with a lower risk of thrombus formation on the LAA device. Overall, an individualized post-procedural antithrombotic regimen should be considered in these patients.

STUDY LIMITATIONS. No causality can be proven because of the nonrandomized, retrospective nature of our study. Even if each center acquired the data prospectively, there may have been an inherent bias in this retrospective collection because centers with fewer or with more complications may have been omitted. There was some heterogeneity regarding device, therapy, and imaging, but this reflects current practice at a national level. Analyzing homogeneous subgroups in this setting is probably unrealistic, and we intended to obtain a global picture of patients

treated with LAA closure in our country. Device-associated thrombus was possibly underdiagnosed because of a difference in post-implantation surveillance and the variations in imaging technique (TEE, CT, or 4-dimensional CT) for screening thrombus on the device among the 8 centers. Underdiagnosis or overdiagnosis of device-related thrombus may result from self-reported imaging results. We were not able precisely to study the temporal proximity relationship between the thrombus and the subsequent embolic event, or to determine that the thrombus directly resulted in a stroke, because, among other reasons, we were unable to establish the length of time that the thrombus had been present when it was identified. Significant heterogeneity was seen between patients with Watchman and Amplatzer devices. Definite conclusions for comparisons between devices would not be appropriate, even though multivariable analysis has been done, because it would not eradicate the confounding variables between these groups. Antithrombotic regimens after LAA closure were also not standardized, and that may have led to differences in incidence of thrombus on the device and adverse events. We did not analyze post-stroke magnetic resonance imaging or CT images to determine whether strokes were likely to be embolic in mechanism or related to earlier vascular disease. Finally, the number of events was relatively low, considering the number of variables in the multivariable analysis, but this may be appropriate for adequate control of confounding in such a study (29).

CONCLUSIONS

Thrombus formation on devices is not uncommon after LAA closure. It is a consequential finding because it is strongly associated with a higher risk of strokes and TIA during follow-up. Therefore, active screening for early detection and treatment of

device-associated thrombus should be performed during post-implantation surveillance. Older age and history of ischemic stroke are clinical features predictive of device-related thrombus. DAPT and OAC at discharge may be associated with a lower risk of thrombus formation on the device. The association between thrombus formation on the device and later strokes, and an optimal antithrombotic regimen that considers individual risks of device-related thrombus after LAA closure, needs to be evaluated in larger, prospective, randomized studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Transcatheter LAA occlusion has emerged as an alternative strategy for stroke prevention in patients with AF who are poor candidates for long-term OAC. Thrombus formation on the device is not uncommon in patients with AF treated by LAA closure.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Thrombus formation on the device after LAA closure is strongly associated with a higher risk of ischemic stroke during follow-up. Therefore, active screening for early detection and treatment of device-associated thrombus should be performed during post-implantation surveillance.

TRANSLATIONAL OUTLOOK: Further studies are still needed to characterize the patients who are optimal candidates for LAA for stroke prevention and the best antithrombotic regimen that considers individual risks of device-related thrombus after LAA closure.

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