Antithrombotic Therapy and Device-Related Thrombosis Following Endovascular Left Atrial Appendage Closure

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Abstract

Left atrial appendage closure (LAAC) is increasingly performed for stroke prevention in patients with nonvalvular atrial fibrillation, especially for those who cannot tolerate or are ineligible for oral anticoagulation (OAC). After device implantation for LAAC, different antithrombotic regimens with varying duration of therapy are currently employed. Such selection depends on patients' risk of bleeding and physicians' choice. Device-related thrombosis (DRT) remains one of the Achilles heel of LAAC, and the etiology remains incompletely understood. Dual antiplatelet therapy (DAPT) and new OAC (NOAC) may have similar safety and DRT occurrence in real-world LAAC registries compared to warfarin and aspirin. Device imaging surveillance should be routinely performed to assess for DRT, which if diagnosed, should be treated aggressively as it is associated with higher thromboembolic risks. Given the uncertainties and therapeutic dilemma, we aimed to provide an in-depth discussion on the options and rationale of antithrombotic therapy post-LAAC.

Condensed Abstract

Left atrial appendage closure (LAAC) is increasingly performed for stroke prevention in patients with nonvalvular atrial fibrillation, especially for those who cannot tolerate or are ineligible for oral anticoagulation (OAC). After device implantation for LAAC, different antithrombotic regimens with varying duration of therapy are currently employed. Device-related thrombosis (DRT) remains one of the Achilles heel of LAAC. Dual antiplatelet therapy (DAPT) and new OAC (NOAC) appear to have similar safety and DRT occurrence in registries compared to warfarin. Given the uncertainties and therapeutic dilemma, we aimed to provide an in-depth discussion on the options and rationale of antithrombotic therapy post-LAAC.

Abbreviations

ACP: Amplatzer cardiac plug

AF: atrial fibrillation

CTA: computed tomography angiography

DAPT: dual antiplatelet therapy

DRT: device-related thrombus

LA: left atrium

LAA: left atrial appendage

LAAC: left atrial appendage closure

LVEF: left ventricular ejection fraction

LUPV: left upper pulmonary vein

NOAC: new oral anticoagulant

OAC: oral anticoagulant

RCT: randomized controlled trial

SAPT: single antiplatelet therapy

TEE: transesophageal echocardiography

TIA: transient ischemic attack

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated lifetime prevalence of 25% after age 40 (1). The worldwide prevalence of AF in 2010 was estimated at 0.5% or 33.5million individuals in the Global Burden of Disease study (2), with prevalence projected to increase dramatically over the next few decades. AF increases the risk of stroke by 5-fold, heart failure by 3-fold, and dementia and mortality by 2-fold (3). Oral anticoagulant (OAC) therapy was established as first-line for thromboembolic stroke prevention, and while the non-vitamin K antagonist OAC (NOAC) agents are at least as efficacious as warfarin in stroke and systemic embolism prevention, the major bleeding rates remained high at 3-4% annually, and any bleeding events were ~20% annually in randomized controlled trials (RCT) (4). Bleeding and perceptions of increased risk of bleeding are significant drivers for under-treatment with OAC in clinical practice, where ~50% of AF patients with guidelines-indications for OAC were untreated (5). Local strategies to directly exclude the left atrial appendage (LAA) have been explored for over 5 decades since it is the source of thrombi in ~90% of cases (6).

Two key RCTs, PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) have helped established the safety and efficacy of the WATCHMAN device (Boston Scientific, Natick, MA) for stroke prevention in patients with non-valvular AF who were eligible for OAC (7). Based on the early successes of these studies, percutaneous LAA closure (LAAC) became rapidly adopted as a second-line stroke preventative strategy especially for patients deemed ineligible or intolerant of OAC. However, LAAC in these patients deemed "contraindicated" to OAC lacks an equivalent evidence base from completed RCTs.

Furthermore, alternative post-LAAC antithrombotic regimens excluding warfarin to minimize device-related thrombosis (DRT) have not been studied in RCT. Nevertheless, in the real-world (especially outside of the United States), the use of antiplatelet therapy post-LAAC became widely utilized, as most of the treated patients were contraindicated to OAC and therefore lack an alternative. In this contemporary review, an in-depth discussion on the options and rationale of antithrombotic therapy and associated DRT post-LAAC are explored.

Animal histopathology studies post-LAAC

The healing process of LAAC remains incompletely understood. Similar to other implanted devices in the human body, there is a requisite time for endothelialization of the device that are exposed to circulating blood. Schwartz investigated the healing process with WATCHMAN in 9 dogs, euthanized at 3 time-points. At day-3, histopathology revealed a thin layer of fibrin covering the device membrane that was exposed to blood circulation. At day-45, the device membrane had an organized neo-endocardial surface on the LAA side, with an extension of the ingrowth into the left atrium (LA) wall. At day-90, fibrous tissue pannus covered the fabric membrane, which had a monolayer of endothelial-like cells that were covering a healthy neo-endocardium. The woven fabric and metallic center of the device were visible and there were thin tissue covering these sites. Hearts from humans who died at 39, 200, 480, and 852days after WATCHMAN implantation (non-device-related deaths) were also examined; the gross and histopathologic findings in humans were similar to those in day-90 animals (8).

Bass studied the Amplatzer Cardiac Plug (ACP)in 10 dogs with immediate, 30 and 90-day follow-up by echocardiography, angiography, and pathological examination (9). On

histopathology, the atrial part of the device was covered by a stable mature neointima, with diffuse ingrowth of mature fibrous connective tissue embedded in the device and within the surface neointima at 90days.

Kar performed a histopathologic comparison of WATCHMAN and ACP in 6 dogs (10). At 28days, the atrial surface of WATCHMAN and the central screw hub were completely covered by neo-endocardial tissue. For ACP, the disc appeared to be in loose contact with the LA wall, and only a small portion of the disc surface was covered by neo-endocardial tissue (with less coverage of the inferior disc edge and end-screw hub). The short duration of follow-up, differences in implantation techniques, and small number of animals, may have influenced the these results.

In summary, endothelialization of LAA devices in dog models appeared complete by 90days. The timeline in humans for complete endothelialization may be protracted compared to dogs, but this has not been studied. Furthermore, there may be significant inter-individual variability, which adds to the uncertainty on duration of antithrombotic therapy during this vulnerable time for DRT before complete endothelialization. Of note, there were anecdotal reports of late incomplete endothelialization in explanted WATCHMAN as late as 10months post-implant (11), raising caution that duration of antithrombotic therapy should be individualized and perhaps monitored.

Warfarin post-LAAC and the risk of DRT and stroke

Both PROTECT-AF and PREVAIL RCTs were designed in the era before direct OAC agents, when warfarin was considered the treatment-of-choice for AF stroke prophylaxis. After

successful WATCHMAN implantation with peri-device leak <5mm, patients were treated with warfarin and aspirin (81mg/d) for 45days, followed by aspirin (325mg/d) and clopidogrel (75mg/d) to 6months, and then aspirin (325mg/d) alone (12). This regimen intended to provide antithrombotic coverage until endothelialization became complete, was largely empiric and partially supported by the preclinical dog studies that showed complete endocardial coverage of WATCHMAN at 45days with warfarin (8). In the PROTECT-AF study, 86.8% of patients in the WATCHMAN arm discontinued warfarin at 45days, 92.2% at 6months, and 93.2% at 1year. The remainder continued warfarin due to residual peri-device leak or physicians' discretion. The incidence of DRT in PROTECT-AF with this regimen was 4.2%, and stroke incidence attributed to DRT was 0.6%. The device thrombus-associated annualized stroke rate was 0.3%/100patient-years (13). In PREVAIL, following successful implant, 92.2%, 98.3%, and 99.3% of patients were able to discontinue warfarin after 45days, 6months, and 12months, respectively, but the incidence of DRT was not reported (14). This post-thrombotic regimen is now considered the "default" for patients able to tolerate short-duration of warfarin, which represents the most robust data from FDA registration trials. Other antithrombotic regimen post-LAAC in the United States is considered off-label.

Of note, in PROTECT-AF, DRT occurred more commonly at the 6-month and 12-month follow-up trans-esophageal echocardiogram (TEE) as opposed to 45-day (15), again raising the concern of delayed endothelialization in some patients, and late development of DRT after cessation of OAC or dual antiplatelet therapy (DAPT).

Real-world usage of non-warfarin regimens post-LAAC and risks of DRT

The most common indication for LAAC is prior bleeding on OAC/NOAC or patients deemed at high-risk of bleeding with these agents. However, this represents a conundrum for DRT prevention after LAAC in patients considered contraindicated to OAC, which is the primary indication for LAAC outside of the United States, since these patients may not tolerate even brief OAC administration post-LAAC. Current European device labeling permits the use of antiplatelet therapy after WATCHMAN and ACP/Amulet implantation, which is the most commonly adopted post-antithrombotic strategy in Europe. Table 1 lists recent studies that addressed the incidence of DRT with various antithrombotic regimen. Of note, there are several limitations with these non-randomized studies, with potential under-reporting and confounding errors. The rigor and frequency of screening with TEE in these studies were not as stringent as randomized trials. Furthermore, there were no adjusted analyses performed to detect differences in DRT rates between different post-LAAC antithrombotic therapies.

Of the various non-warfarin regimen, DAPT is the most commonly utilized, extrapolating from decades of experience with patent foramen ovale and atrial septal defect occluders. The prospective ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) registry (n=150) showed DRT incidence of 4.0% with DAPT post-WATCHMAN and thromboembolic event-rate of 2.3%/yr, in patients contraindicated to OAC (16). In the EWOLUTION registry of 1005 WATCHMAN implants, 60.2% received DAPT, 7.0% single antiplatelet therapy (SAPT), 15.4% warfarin, 10.8% NOAC, and 6.5% no antithrombotic post-LAAC. The average incidence of DRT was 2.3%, with no significant difference between each of these regimens (17). In the retrospective ACP multicenter study, the incidence of DRT was 3.2% among the TEEs adjudicated by core-laboratory, and DRT was not associated with thromboembolic events (18). In the prospective multicenter Amulet post-

marketing registry of 1,088 patients, 54.3% were administered DAPT, 23.0% SAPT, 18.9% OAC, and 2.0% no antithrombotic post-LAAC. Surprisingly, the incidence of DRT was only 1.5% at the first TEE follow-up in 673 patients (19).

With direct OACs, 2 studies assessed the efficacy of brief direct OAC administration post-LAAC, with low rates of bleeding, stroke and DRT (20,21). In the retrospective study by Enomoto, 214 patients received direct OAC post-WATCHMAN (46% apixaban, 46% rivaroxaban, 7% dabigatran, and 1% edoxaban). The incidence of DRT was 1.4% compared to a control group of 212 patients on warfarin ($p>0.99$). There was no significant difference in the rate of peri-procedural complications (2.8% vs 2.4%; $p>0.99$) or post-procedural bleeding (0.5% vs 0.9%; $p=0.6$), for NOAC versus warfarin, respectively (21). In EWOLUTION, 109 patients received direct OAC after WATCHMAN (dabigatran, rivaroxaban, and apixaban) with DRT incidence of 1.3% (20). Despite the small number of patients studied, direct OAC post-LAAC appeared feasible, although there is inadequate data to support a particular agent or dose.

These data have led to a change in international LAAC device labeling, which now recommends 3-month DAPT or direct OAC post-LAAC, if the standard regimen with 45 days of warfarin followed by DAPT up to 6 months is not feasible. The randomized ASAP-TOO (Assessment of the Watchman device in patients unsuitable for oral anticoagulation) trial was recently launched, specifically comparing WATCHMAN vs. standard care (single or no antiplatelet therapy) for patients ineligible for warfarin, and incorporates a 3-month DAPT (aspirin and clopidogrel) regimen post-LAAC (22). This is a large study randomizing 888 patients from 100 global sites, with primary efficacy endpoint of time to occurrence of ischemic stroke or systemic embolization. Patients will be followed clinically for 5 years, and routine TEE will be performed at 3 and 12 months post-LAAC, which will be critical to assess the safety of

DAPT after WATCHMAN implantation. The ongoing Amulet IDE study (n=1800) randomizing WATCHMAN to Amulet includes a DAPT regimen post-Amulet for patients deemed eligible for OAC. Both these studies mandate routine TEE follow-up, and will provide robust data on the incidence of DRT with DAPT post-LAAC.

SAPT post-LAAC had also been used, particularly in patients with very high bleeding risks, such as those with prior intracerebral bleeding or cerebral amyloid angiopathy. In a single-center 110-patient study from Denmark, 87.8% who had ACP/Amulet implantation were treated with SAPT and 12.2% with DAPT, and the incidence of DRT was only 1.9% (23). In a larger retrospective series from 9 French centers, 171/487 (35.8%) patients received SAPT and 37/487 (7.7%) received no antithrombotic therapy after WATCHMAN or ACP/Amulet. Amongst the 337 patients with imaging follow-up with TEE or CTA at mean 2.8months, the incidence of DRT was 7.2%, which appeared higher than earlier series (24). Of note, only 4.3% received the FDA-recommended warfarin regimen. Importantly, more patients with DRT were not treated with any antithrombotic therapy compared to those without DRT (15.4% vs. 4.5%, p=0.02). Patients treated with DAPT (HR 0.1, p=0.03) or OAC (HR 0.26, p=0.02) post-LAAC had much lower hazard ratio for DRT in multivariable analysis. Furthermore, the presence of DRT was associated with higher risk of stroke/TIA (HR 4.4, p=0.04). Overall, this study raised concerns about SAPT and no antithrombotic therapy with regards to DRT and stroke/TIA risk. Larger studies and imaging follow-up are required to further evaluate these seemingly suboptimal regimens. The STROKE-CLOSE (NCT02830152) study (n=750) is randomizing patients with prior intracranial hemorrhage to Amulet (followed by aspirin alone) or standard medical therapy without LAAC, which will provide invaluable data on use of SAPT post-LAAC.

Overall, DAPT and NOAC regimens post-LAAC appeared safe and comparable to warfarin in real-world registries in terms of incidence of DRT and thromboembolic events. However, these observations were derived from non-randomized studies and have several limitations. Future results from large randomized studies such as ASAP-TOO, Amulet IDE, STROKE-CLOSE, and CLOSURE-AF (NCT03463317) (n=1400) will more comprehensively address whether antiplatelet therapy is safe and effective post-LAAC in patients contraindicated for OAC. At the meantime, feasible antithrombotic regimens post-LAAC for OAC eligible and ineligible patients are described in Figure 1, with the choice dependent on the patients' bleeding risks and physicians' preference. DAPT is the most commonly chosen regimen in patients contraindicated to OAC, but the duration of therapy varies widely (ranging from 1 to 6 months), prior to stepping down to aspirin alone (for total of ≥1year). Of note, options D & E are inadequately studied, and should only be considered for patients at very high risk of bleeding.

Predictors of device-related thrombosis

A systematic review of 30 LAAC studies highlighted a correlation between DRT and the frequency of follow-up imaging (25), stressing the need for standardizing follow-up of LAAC to enable comparisons between devices or antithrombotic regimen. It is likely that many factors culminate in DRT, including procoagulant patient-specific factors, antithrombotic choice post-LAAC, and device and implant-specific factors (Table 2). There are four patient-specific factors that appear relevant: (1) tendency to form LA clot, (2) tendency to bleed (which may limit medical bail-out options), (3) compliance and responsiveness to medical therapy, and (4) ability to endothelialize the device. Very few studies examined the risk factors for DRT and revealed

different conclusions. Left ventricular ejection fraction (LVEF) <40% was the only parameter identified in more than one series (26,27). Female sex, smoking, higher CHA_2DS_2-VASc score, spontaneous echocardiographic contrast (SEC), pre-existing LAA thrombus, and LAA peak emptying velocity were identified risk factors (18,26,27).

Differences in implanting techniques and mechanisms of closure in LAAC devices may impact DRT. Epicardial closures systems such as the Lariat device (SentreHEART, Redwood City, CA) may have lower DRT (reported at ~2%) (28) since there is no device contact with blood circulation, but there are no prospective studies comparing to intracardiac endovascular LAAC devices. Interestingly, for endovascular devices, no clear correlation between device size and DRT was reported (18). Endovascular devices typically have a covering fabric and an exposed central screw-hub. Thrombus was preferentially reported to form on the exposed metallic screw-hub of the ACP (26,29), prompting its redesign and hub recession in the 2nd generation Amulet device. In the Amulet Post-Marketing Registry, DRT incidence was only 1.5% (19), however, only ~60% of patients had TEE follow-up (mean 67days). Furthermore, another small (n=24) single-center experience with Amulet reported DRT incidence of 16.7%; with all 4 cases having thrombus in the cul-de-sac created between the disk and the left upper pulmonary vein ridge (27), confirming previous suspicion that deep device implantation can predispose to DRT (25). The Wavecrest device (Coherex Medical, Salt Lake City, UT) was described to have a less thrombogenic covering fabric, however, prospective studies will need to be performed to confirm this theoretical benefit.

Peri-device leak due to incomplete occlusion of the ostium of the LAA can connect the residual LAA pouch to the systemic circulation. Based on surgical experience, incomplete closure and remnant LAA stump >1cm was associated with thrombus formation and

thromboembolic events (30,31). Residual flow around a device into a stagnant LAA pouch may result in turbulent blood flow and enhance platelet adhesion and clot formation. Small ostial gaps <5mm are likely too small for thrombus to escape into the systemic circulation, as shown by lack of correlation between peri-device leaks and thromboembolic events (18,32). On the other hand, the presence of large leaks >5mm typically leads to continuation of OAC, which may mask contribution to DRT formation from residual leaks.

Imaging assessment of device-related thrombosis

Thrombus is described as a discrete echocardiographically dense mass with well-defined borders, distinct from endocardium and visualized throughout the cardiac cycle. The surface of the thrombus may appear smooth or irregular, but more often may be laminar or pedunculated and partially mobile, where its motion independent of myocardium distinguishes it from artefact. Large thrombus (>10mm) and degree of mobility may be risk factors for embolization (25).

Following implant, device endothelialization occurs over the LA surface and extends over the adjacent endothelium (Figures 2A, B and D). It is consistent with the process of normal healing and should not be confused with thrombus. Endothelial tissue typically has a smooth uniform appearance extending over the device surface becoming continuous with LA endothelial tissue. DRT appears to present at two key sites. It may be seen over the LA surface of the device, predictably associated with the central screw/insert protruding from the surface or fabric insert site. Secondly, incomplete lobe coverage may result in recesses or exposed proximal trabeculation where slow flow creates a nidus for thrombus formation.

In the clinical setting, most centres perform TEE at 6-12 weeks and only repeating the TEE in cases of abnormal findings (significant residual leaks >3-5mm, thrombus, device malposition/displacement) (25). Consideration should be given to potential high-risk features for thrombus formation at the time of implantation and follow-up imaging (Table 2). These include dense SEC or an associated low-flow state including severe LV dysfunction, and regions of trabeculation that remain exposed post-LAAC. Such high-risk features should prompt additional late TEE imaging at 6–12 months. The FDA label for WATCHMAN required TEE be performed at 45days and 12months, and if thrombus is observed then warfarin is recommended until resolution of thrombus is demonstrated by TEE. We support this recommendation, with the flexibility of performing the first surveillance imaging at 6-12 weeks (preferably after cessation of OAC/NOAC/DAPT to allow detection of DRT after stepdown of antithrombotic therapy).

While the reference imaging modality for the assessment of DRT is TEE, studies have demonstrated the clinical utility for CT angiography in detecting DRT (33,34). However, these studies involved small numbers with very low incidence of reported DRT and limited head-to-head comparison with TEE.

Recommended management of device-related thrombosis

Published data on the management of DRT are limited. In a recent review, Lempereur reported on the treatment of DRT in 40 cases from clinical trials, multicentre or single-center registries and case reports (25). In this study, the incidence of DRT was 3.9%, and 7.3% suffered stroke/TIA, highlighting the risks of thromboembolism with DRT and the need to treat the thrombus. Furthermore, in the study by Fauchier, DRT was an independent predictor of

stroke/TIA (HR 4.4) (24). Low-molecular weight heparins (LMWH) (45.5% of cases) and OAC (36.4% of cases) were the most frequently used strategies to treat DRT. The mean duration of treatment was 2 weeks for LMWH and 3 months for OAC. Treatment was highly effective with a thrombus resolution rate of 100% with LMWH and of 89.5% for OAC. Recurrence rate of DRT after treatment was low (2/40), but the extent of follow-up was poorly defined in the reported cases. Also, in a recent European Heart Rhythm Association survey, LMWH (43% of 33 European LAAC centers) and OAC (29% of centers) were the most preferred treatments of DRT (35).

Data on NOAC for DRT treatment is sparse, with dabigatran and apixaban shown to resolve isolated cases of DRT (36-38), and incomplete resolution in some cases (39). Moreover, dabigatran was shown to be ineffective in mechanical heart valves and against thrombosis triggered by foreign materials (40). Thus, NOAC should be used cautiously in the setting of a newly implanted mechanical device.

Recommendations for management of DRT is summarized in Table 3. The most common treatment strategy is warfarin for 8–12weeks (aiming INR 2–3) in patients not already on OAC at the time of DRT diagnosis. For patients already on warfarin, intensifying INR to 2.5–3.5 is recommended. The addition of low-dose aspirin to warfarin may be considered if bleeding risk is low. The use of full-dose NOAC for 8-12weeks may also be considered, with or without the addition of low-dose aspirin. If the thrombus is very large (>15mm) and mobile, the embolic risk may necessitate treatment with LMWH and repeat imaging within 2weeks to ensure response to therapy. Intravenous heparin can be an alternative to LMWH in patients with renal failure. Rarely, surgical removal of the thrombus and LAA device may be required in cases of very large

device thrombi, recurrent embolization from DRT, or failure of OAC treatment (41). A suggested algorithm for screening and management of DRT is described in Figure 2.

Once DRT treatment is initiated, repeat imaging by TEE or CT angiography should be performed to document thrombus resolution before stopping the antithrombotic treatment (at 8–12weeks). Furthermore, delayed imaging in 3–6months should be considered to survey for thrombus recurrence after treatment is stopped.

Conclusion and Future Directions

In summary, although OAC remains the first-line therapy for stroke prevention with nonvalvular AF, a significant proportion cannot tolerate or are ineligible for OAC. Thus, LAAC is an excellent alternative and is widely adopted as second-line therapy. Post-LAAC, different antithrombotic regimens are currently utilized with differing duration of therapy. These non-warfarin strategies have not been studied in RCTs, but DAPT and NOAC appeared to have similar safety and DRT occurrence in real-world LAAC registries. Aside from the choice of post-LAAC antithrombotic therapy, the occurrence of DRT may have other important device/implant-specific and patient-specific risk factors. DRT remains one of the Achilles heel of LAAC, and device imaging surveillance should be routinely performed to aid diagnosis and management of DRT, since it is associated with higher thromboembolic risks. Ongoing large RCTs are addressing the safety and efficacy of LAAC in different cohorts of OAC-contraindicated patients, which will further elucidate the role of antiplatelet therapy post-LAAC. Novel devices with less thrombogenic fabric may also reduce the risk of DRT, but clinical trial results are needed to validate such claims.

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Table 1: Overview on recent LAAC studies employing various non-warfarin drug regimens post-procedurally

	Lempereur et al (25)	EWOLUTION registry (17)	EWOLUTION Registry (20)	ACP Registry (18,42)	Amulet Registry (19)	Reddy et al (21)	Korsholm et al (25)	Fauchier et al (24)
Device	WM, ACP, Amulet	WM	WM	ACP	Amulet	WM	ACP, Amulet	WM, ACP, Amulet
Number of patients	2118	605	109	1047	1088	214	110	469
Registry design	retrospective, metaanalysis	prospective	prospective	retrospective	prospective	retrospective	retrospective	retrospective
Drug regimen	N/A	DAPT	NOAC	SAP, DAPT, OAC	SAP, DAPT, OAC	NOAC	SAP, DAPT	OAC, DAPT, SAC, none
Follow-up	6-24mth	12mth	3mth	3-24mth	3mth	4mth	2.3yr	13mth
Rate of DRT	3.9%	4.0%	1.3%	4% (3.2% adjudicated)	1.5%	0.9%	1.9%	7.2%
Bleeding rate	N/A	2.5%@1yr	1.9% @ 3mth	5.7% @ 1yr	4% @ 3mth	0.5%	3.8%/yr	3.8%
Stroke rate	0.28%	1.4%@1yr	0% @ 3mth	2.1% @ 1yr	1.4% @ 3mth	0.5%	2.3%/yr	4.0%

N/A, not available

DAPT, dual antiplatelet therapy

NOAC, new OAC

SAP, single antiplatelet therapy

OAC, oral anticoagulant

DRT, device-related thrombus

Table 2: Potential risk factors for device–related thrombus

Category	Mechanism	Specific details
Unmodifiable Patient Factors	Increased clot formation	Echocardiogram parameters: 1) LVEF <40% 2) Spontaneous echo contrast 3) Low LAA peak emptying velocity Hematological: relative platelet count elevation Female sex High CHA_2DS_2VASc score
	Reduced clot dispersion	Medication responsiveness Medication acceptability (bleeding)
	Slow device endothelialization	Unmeasurable/unpredicatable even at young age
Post-procedural medication	Potency of strategy Compliance	Choice of SAPT/DAPT/NOAC/OAC/LMWH 1) Subtherapeutic INR 2) Non-compliance 3) Early medication discontinuation
Mechanical Factors	Implantation result Device Peri-procedural	1) Deep implant - forming neo-appendage 2) Failure of disc apposition 3) Residual leak 1) Intracardiac vs. extracardiac devices 2) Exposed screw 1) Thrombus on device/wire during implant

Table 3: Recommended treatment and duration for DRT management

Treatment Options	Duration	Comments
VKA (25,35)	8–12 weeks	Aim for INR 2–3 For patients already on warfarin, target INR 2.5–3.5 Consider combination with ASA*
NOAC (36-38)	8–12 weeks	Full dose NOAC, limited experience Apixaban, rivaroxaban (avoid dabigatran) Consider combination with ASA*
LMWH (25,35)	2–4 weeks	Consider in cases of large thrombi IVH is an alternative to LMWH in renal failure Consider combination with ASA*
Surgical excision (41)		Consider if therapy failure, recurrent embolization, or very large thrombi

*Combination with ASA should be avoided if bleeding risk is considered high.

LMWH: low-molecular weight heparin; IVH: Intravenous heparin; NOAC: new oral anticoagulant; VKA: vitamin K antagonist;

Figure Legend:

Figure 1: Feasible choices of antithrombotic therapy after LAAC according to eligibility for short-term full-dose OAC post-LAAC. Note: options D and E are less well supported by clinical data, and should only be considered for patients at very high-risk for major bleeding.

Figure 2: Images A, B, D; (A) 3D TEE, ACP device at time of implantation, (B) same device six months post-implantation now almost entirely obscured by endothelial tissue growth, (D) 2D TEE demonstrating endothelialization where a thin homogeneous uniform layer is seen (white arrows). (C) WATCHMAM device on follow-up 2D TEE showing a pedunculated non-mobile thrombus (*) extending over the lateral surface of the device towards the central insert (Image courtesy of Dr. John Foran, Royal Brompton Hospital). (E) (3D TEE) and (F) (2D TEE) of the same WATCHMAN device, showing a recess (red arrows) adjacent to the LA surface of the device containing regions of trabeculation and associated small mobile thrombus white asterisks and arrow.

LSPV: left superior pulmonary vein, PA: pulmonary artery, MV: edge of mitral valve annulus and leaflet.

Figure 3: Suggested algorithm for screening and management of DRT

Figure 1.

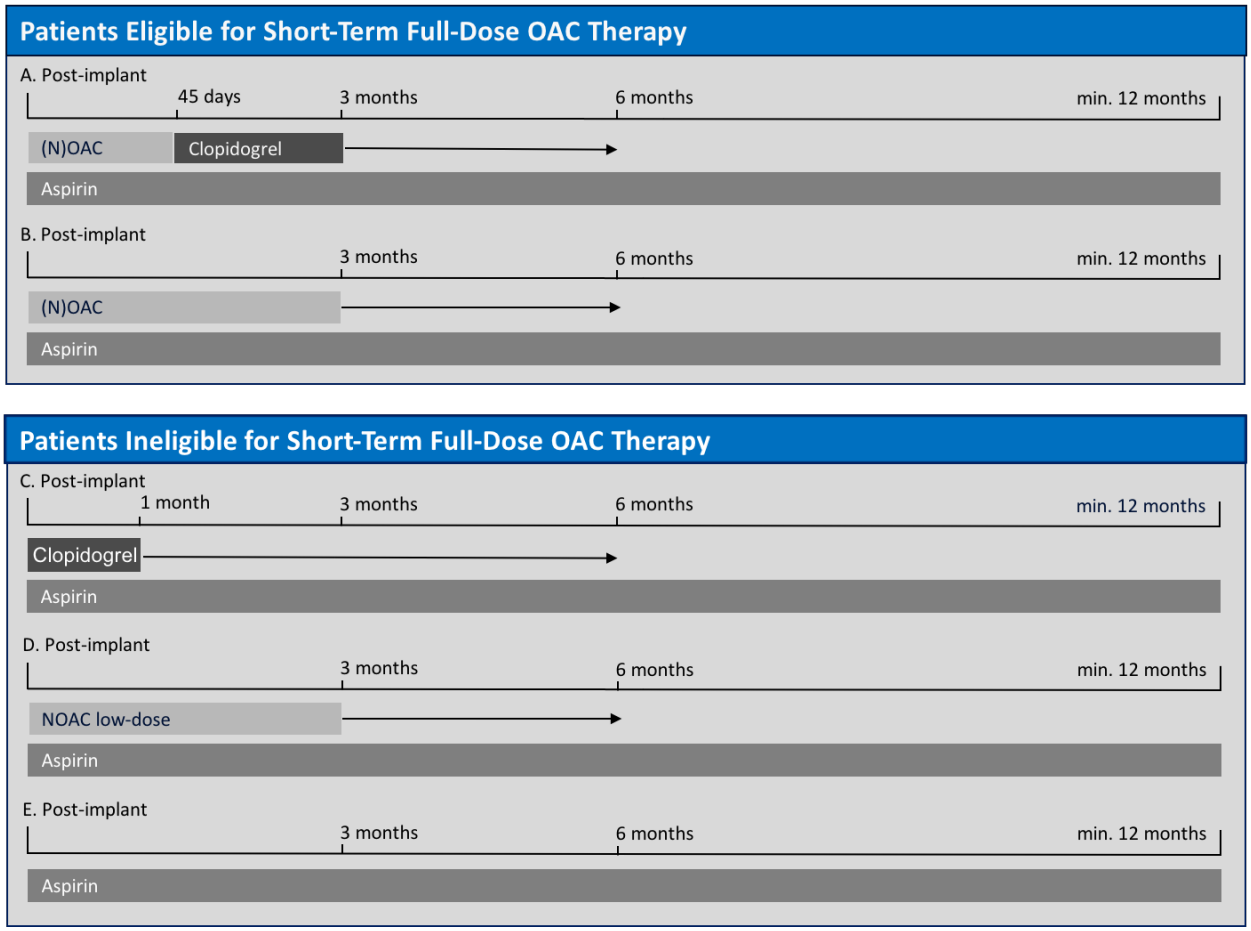

Patients Eligible for Short-Term Full-Dose OAC Therapy
A. Post-implant
45 days
3 months
6 months
min. 12 months
(N)OAC
Clopidogrel
Aspirin
B. Post-implant
3 months
6 months
min. 12 months
(N)OAC
Aspirin
Patients Ineligible for Short-Term Full-Dose OAC Therapy
C. Post-implant
1 month
3 months
6 months
min. 12 months
Clopidogrel
Aspirin
D. Post-implant
3 months
6 months
min. 12 months
NOAC low-dose
Aspirin
E. Post-implant
3 months
6 months
min. 12 months
Aspirin

Figure 2.

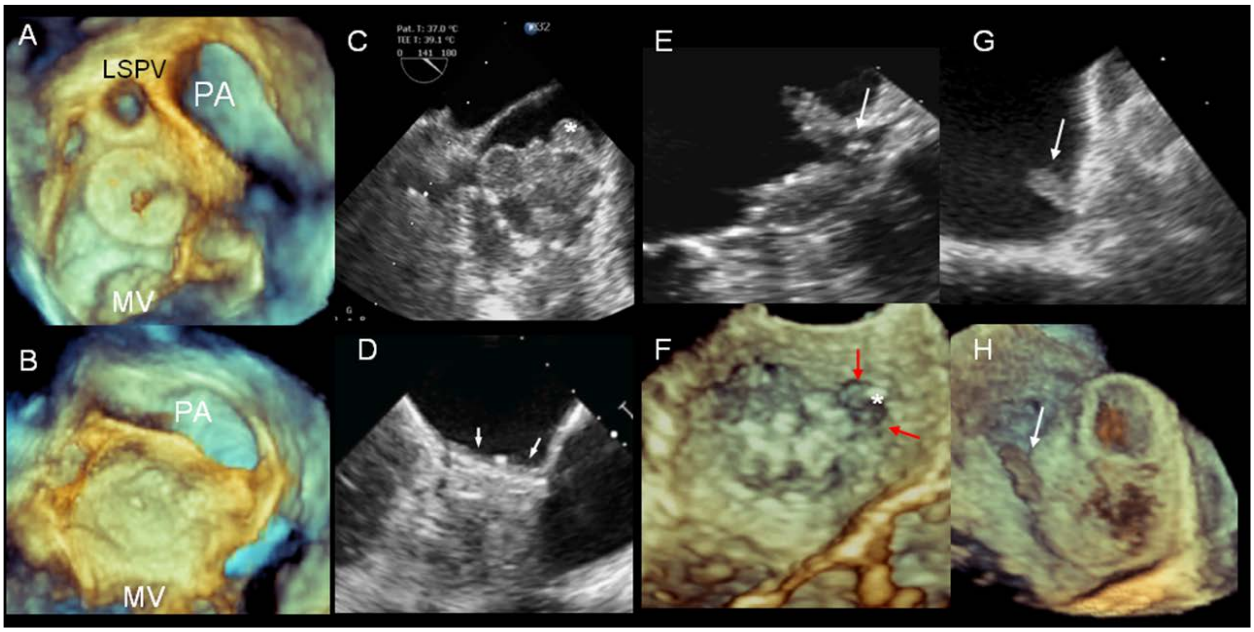
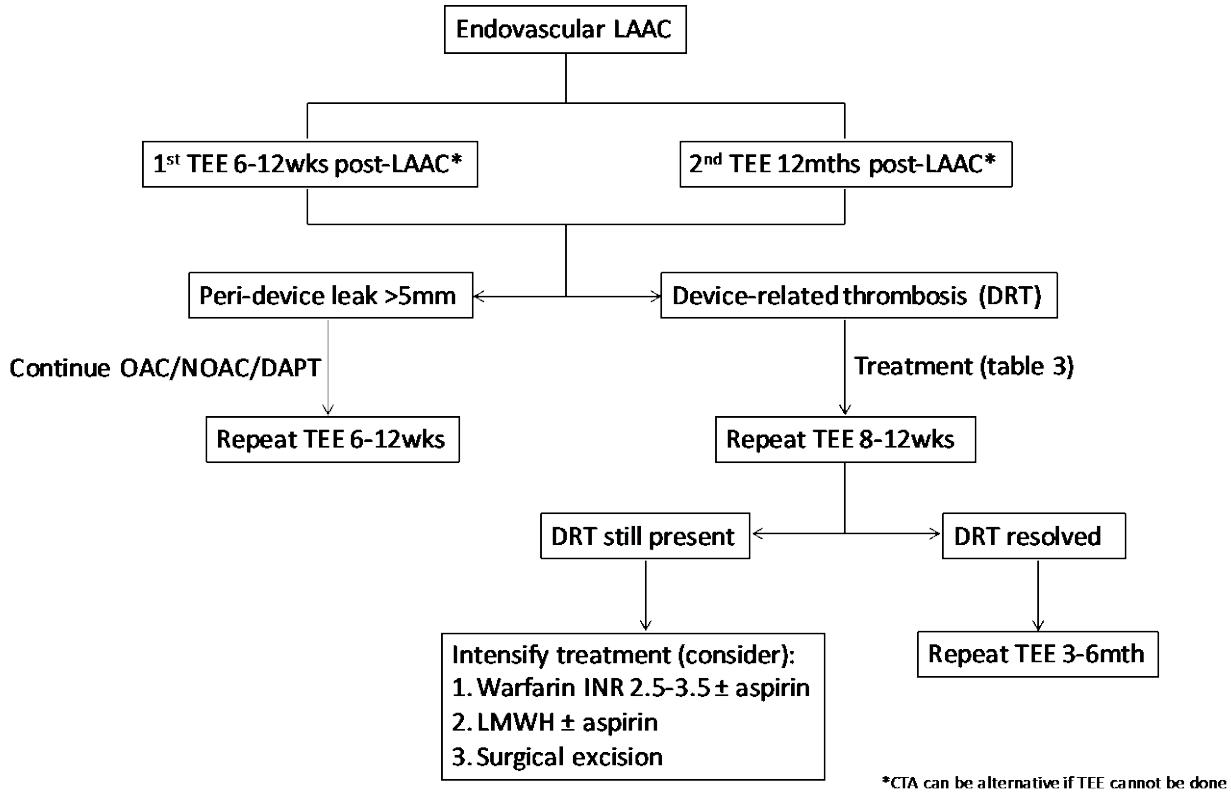


Figure 3.


Endovascular LAAC
1st TEE 6-12wks post-LAAC*
2nd TEE 12mths post-LAAC*
Peri-device leak >5mm
Device-related thrombosis (DRT)
Continue OAC/NOAC/DAPT
Treatment (table 3)
Repeat TEE 6-12wks
Repeat TEE 8-12wks
DRT still present
DRT resolved
Intensify treatment (consider):
1. Warfarin INR 2.5-3.5 ± aspirin
2. LMWH ± aspirin
3. Surgical excision
Repeat TEE 3-6mth
*CTA can be alternative if TEE cannot be done