Treatment of Persistent Left Atrial Appendage Thrombus in Patients with Atrial Fibrillation on Adequate Oral Anticoagulation: Pathways of Care for All-comers and Heart Failure Patients

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Abstract

In patients with AF, the presence of left atrial/left atrial appendage (LA/LAA) thrombus is related to an increased risk of thromboembolic events. Anticoagulation therapy, either with vitamin K antagonists or novel oral anticoagulants (NOACs) is therefore mandatory in AF with LA/LAA thrombus in order to lower the risk of stroke or other systemic embolic events. Despite the efficacy of these treatments, some patients will have persistent LAA thrombus remaining or may have contraindications to oral anticoagulation. Currently, little is known about the occurrence, risk factors and resolution rate of LA/LAA thrombus in patients who are already under optimal chronic oral anticoagulation, including vitamin K antagonists or NOACs. The common action in clinical practice in this scenario is switching from one to another anticoagulant drug exhibiting a different mechanism of action. Repeated cardiac imaging is then advised within several weeks to visually verify thrombus dissolution. Finally, there is a substantial scarcity of data on the role and optimal use of NOACs after LAA occlusion. The aim of this review is to critically evaluate data and provide up-to-date information on the best antithrombotic strategies in this challenging clinical scenario.

Keywords

AF, left atrial appendage, non-vitamin K oral anticoagulant, novel oral anticoagulants, persistent thrombus, thrombosis, warfarin

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Non-valvular AF is the most prevalent sustained cardiac arrhythmia linked to a high risk of stroke, systemic embolism (SE), heart failure (HF) and all-cause death.[1] Without oral anticoagulation, the age-adjusted risk of AF-related stroke increases fivefold.[2] For decades, oral anticoagulants (OAC) with vitamin K antagonists (VKA) were the standard therapy for AF-associated stroke and SE, with a 64% relative risk decrease in stroke.[3] Because of the narrow therapeutic window of VKAs, it is mandatory for warfarin therapy to stay within adequate therapeutic range as reflected by tests of haemostasis, such as prothrombin time normalised by the international normalised ratio (INR). The time that patients spend in the VKA therapeutic range (TTR) of 65% is rare, even in large randomised trials, while drug compliance and TTR, as expected, are even worse in real life than in randomised controlled trials.[4–6]

Meta-analysis of all four novel OACs (NOACs) reveals a 19% reduction in the incidence of stroke or SE compared to VKA.[7] Left atrial/left atrial appendage (LA/LAA) thrombus is found in 13–19% of AF patients without anticoagulation.[8,9] The EMANATE trial reported 7.1% thrombus formation in anticoagulation-naive AF patients and 3.5–17.8% under VKA treatment.[10] A recent retrospective cohort study showed that, despite anticoagulation for the recommended 3 weeks before cardioversion, a significant proportion of patients (40%) were found to have LA/LAA thrombus (LAT), especially those on warfarin who had a much higher incidence of this finding compared with on NOACs.[11]

In patients with nonvalvular AF, LAA thrombosis increases the risk of thromboembolic events.[12,13] Implications for long-term stroke and thromboembolism risks due to persistent LAT to long-term anticoagulation are poorly understood. Such refractory LAT may become organised over time and pose a lower embolisation risk than newly generated LAT. This theory is reinforced by the fact that, despite reported rates of LAT detection of up to 3.6% among patients on continuous anticoagulation, recorded rates of thromboembolic events after cardioversion are much lower.[14,15] In conclusion, regarding stroke risk, current evidence reveals that both fresh and organised thrombus might be the embolic source. However, because organised thrombus may be challenging to distinguish from the endocardium, a high degree of suspicion might be needed to diagnose an organised thrombus.[16]

Predictors of Left Atrial Appendage Thrombosis Despite Oral Anticoagulation

Factors impacting the occurrence of LA or LAA thrombus despite therapeutic anticoagulation with VKA or NOACs among patients with AF are mainly unexplored. In a recent study, Angelini et al. reported that 7.7% of patients with AF referred for catheter ablation or electrical cardioversion had LA/LAA thrombus verified by transoesophageal echocardiography (TOE), despite receiving a guideline-recommended daily dose of NOAC for the purpose of thromboembolic prevention.[17] Moreover, 5.1% of all patients had an echocardiographic finding of a dense LA/LAA spontaneous echo

contrast, which may precipitate thrombus formation. Finally, they found that this population's significant predictors of LA/LAA thrombus were CHA_2DS_2-VASc score >3 and obesity, providing an OR for thrombus presence of 4.54 and 6.01, respectively. This is concordant with previous data from Bertaglia et al., reporting that 3.6% of patients with AF treated with NOAC for at least 3 weeks had LAT visualised by TOE, and all were located in the LAA.[18] They also found that this finding was not dependent on NOAC type, while patients with LAA thrombus tended to have a mean CHA_2DS_2-VASc score of ≥3, thus suggesting that preprocedural TOE in this group might be considered.

Despite anticoagulant therapy, similar findings were reported elsewhere, confirming the association of high CHA_2DS_2-VASc score and LAT presence and its link to future cerebrovascular events.[19,20] However, this relationship is not that simple because even in patients with non-valvular AF and low CHA_2DS_2-VASc score, elevated plasma homocysteine levels were predictive of LA/LAA thrombus.[21] Similarly, in two Polish cohorts enrolling consecutive AF patients of whom the majority or all were receiving oral anticoagulation, the presence of LA/LAA thrombus was 5.7% and 7.5%, respectively, while persistent and permanent AF, renal dysfunction (estimated glomerular filtration rate <56 ml/min/1.73m^2), lower mean LAA flow velocity and history of vascular disease were established as solid independent predictors of LA/LAA thrombus formation.[22,23]

Interestingly, data derived from the retrospective registry of 820 consecutive patients with AF undergoing TOE who were anticoagulated with apixaban for at least 4 weeks before imaging demonstrated that no thrombi were detected in patients with CHA_2DS_2-VASc score of ≤1.[24]

Furthermore, LAA morphological architecture and function may differentially impact on thrombogenesis of LA in patients with AF.[25] For example, complex LAA morphology characterised by the increased number of LAA lobes was independently associated with LAT, spontaneous echo contrast and stroke in patients with non-valvular AF.[26,27] Similarly, non-chicken wing LAA morphology, according to TOE, was associated with an 11.5-fold higher likelihood of LA/LAA thrombosis in patients with non-valvular AF compared to those having a chicken wing LAA formation.[28] Decreased LAA flow velocity propagates blood stasis within LAA and this phenomenon occurs in AF; thus, it might independently enhance the risk of thrombogenesis.[29,30] Echocardiographic and morphological parameters, such as decreased a-wave rate, increased LA dimensions, atrial sphericity and the degree of atrial fibrosis quantified by late gadolinium enhancement cardiac MRI, were shown to be independently associated with appendage thrombus, thromboembolic events and spontaneous echo contrast in several studies.[31–35] The degree of LA dysfunction in non-valvular AF, such as LA emptying fraction <30% in addition to CHA_2DS_2-VASc score, was a crucial enhancing risk factor for LAT or dense spontaneous contrast in patients with AF.[36] Similarly, contrast retention during the LAA occlusion procedure, LAA cauliflower morphology and reduced left ventricular ejection fraction (LVEF) were independently associated with LA/LAA thrombosis.[37]

Similarly, inappropriately reduced daily dosages of NOACs are likely to enhance the potential for LAA thrombus formation, thus emphasising the need to critically evaluate the pros and cons of NOAC dose reduction in each patient with AF.[38] Finally, some drugs concomitantly used with NOACs, such as antiepileptic medications (phenobarbital, phenytoin and carbamazepine), might reduce the therapeutic efficacy of NOACs, thus facilitating the formation of LAT despite guideline-recommended continuous oral anticoagulation.[39]

Characteristics and Presence of Left Atrial Appendage Thrombus Depending on the LVEF and Presence of Heart Failure

It is recognised that the LA or LAA thrombus can be an essential source of thromboembolism in patients with HF, especially those with a dilated cardiomyopathy phenotype. The anatomical shape of the LAA facilitates haemostasis, which is even more enhanced in cases of poor systolic function and slow flow. Thus, it is a common site for thrombus formation among patients with HF.[40] In the subanalysis of the multicentre, prospective, observational LATTEE registry, it was found that the prevalence of LAT was nearly three-fold higher in patients with HF compared to non-HF patients (12.8% versus 4.4%).[41] As expected, the LAT presence increased as the systolic dysfunction decreased, meaning that HF with reduced ejection fraction was associated with a significantly 4.1-fold greater likelihood of LAT presence (95% CI [3.13–5.46]) compared to non-HF patients. At the same time, this relationship was insignificant in patients with mildly reduced or preserved systolic function. The multivariable regression analysis within the same study revealed that lower LVEF was an independent predictor of LAT formation, whereas LVEF ≤48% was associated with an increased risk of LAT presence. Of note, this study employed chronic anticoagulation in 88% of patients before TOE; 1.5% were using transient anticoagulation, while only 10% were naive to oral anticoagulation. Age ≥75 years and HF were strongly associated with the presence of LAT among patients with non-valvular AF enrolled in the ENSURE-AF trial.[42] Similar findings were validated in a significant meta-analysis pooling 56,660 patients with AF that underwent catheter ablation or electrical cardioversion (ECV). The presence of LAT was 1.3% and 4.9% among those adequately taking OAC, respectively. This study showed that HF was an essential predictor of LAT presence: OR 4.3 among AF patients undergoing ablation and OR 2.8 for those undergoing ECV.[43] Interestingly, the OR for LAT was nearly identical for congestive HF patients in the study by Wu et al. (OR 4.4; 95% CI [1.6–12]).[15]

Novel echocardiographic parameters such as peak LA longitudinal strain (PALS) for LAA thrombus have been recently evaluated among HF patients. Concordantly, in a study that included CHF patients with severely depressed systolic function (LVEF <25%) and sinus rhythm, it was found that LAA thrombus was present in nearly one-third of patients (31.7%), while global PALS was a strong predictor of LAAT (OR 30.4; 95% CI [7.2–128]) for LAAT presence if the measured PALS value was <8%. This study also showed that the tendency for thrombus formation in LAA is significantly enhanced in HF patients with severely depressed systolic function, even in the absence of AF.[44]

Risk factors, predictors or markers of LA/LAA thrombus are summarised in *Figure 1*.

Oral Anticoagulant Strategies in Persistent Left Atrial Appendage Thrombus Among Patients Already on Continuous Oral Anticoagulation

The management strategy in patients with verified LAA thrombus despite therapeutic oral anticoagulation is unclear and mainly based on expert consensus statements or limited case series reports. The recent European Heart Rhythm Association (EHRA) survey conducted among 54 hospital centres showed that in cases of persistent thrombus. In contrast, regarding VKA, most centres would switch VKA in eligible patients to NOAC (42.5% of cases); some would reassess the quality and adherence to VKA in 23.4% of cases. In contrast, 17% would remain on VKA and aim for the higher INR values (2.5–3.5).[45] Similarly, about 6.4% of centres would switch from VKA to low-molecular-weight heparin (LMWH).

Concerning antiplatelet therapies, the same survey showed that adding antiplatelet agents was infrequent, while none of the centres opted for dual antiplatelet therapy (DAPT). Similarly, the switch to unfractionated heparin among enrolled centres was highly uncommon.

On the other hand, when thrombus was present despite chronic NOAC treatment, the EHRA study showed that the most common strategy was to switch from NOAC (regardless of type) to VKA with a target INR of 2.5–3.5 or to switch to VKA with a target INR of 2–3; these two strategies accounted for about half of all management scenarios. Switch from NOAC to LMWH was used among 6.4–12.8% of participating centres, depending on the NOAC type, with the highest switching rate registered for apixaban and lowest for edoxaban. When NOAC to NOAC substitution was opted for, apixaban and dabigatran were the most commonly tried replacement NOACs. Similarly, the EHRA survey showed that the timing of repeated imaging after the change in OAC remains heterogeneous across centres.[45] Nearly half of the centres would repeat imaging 3–4 weeks after the antithrombotic switch, while one-third would repeat imaging after 5–6 weeks. About 11% of centres would opt for delayed imaging arranged >2 months following the antithrombotic switch.

Real-world data might help shed light on the practical use of antithrombotics to resolve refractory LATA thrombus in patients with AF. For example, Faggiano et al. analysed data from 8,888 consecutive patients with AF who underwent TOE in two high-volume clinical centres. Most patients with identified LAA thrombus (3% of the total cohort) were on OAC for at least 3 weeks before index imaging. Their study showed that a VKA for LAA thrombus resolution was prescribed in 52%, NOAC in 27%, and LMWH in 18.5% of patients. Two-thirds of these patients received repeat TOE within a median time of 39 days, while one-third did not receive any follow-up imaging study. Importantly, thrombus resolution was achieved in 67% of all patients who underwent repeated TOE, while no significant difference in efficacy was established between VKA and NOACs.

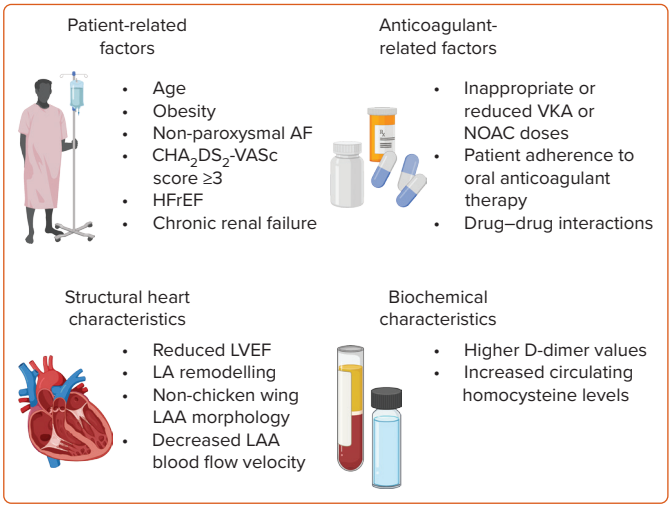
Kolakowski et al. specifically reported on chronically anticoagulated patients for AF or atrial flutter and still had LAA thrombus detected by the TOE.[46] They showed that nearly 52% of patients had LAA thrombus dissolution regardless of the number of treatment cycles employed. In contrast, any change in treatment (switch to a different OAC) was associated with increased odds of success. However, it is unclear whether any particular treatment strategy is more effective than the other. Additionally, the authors showed that several anticoagulation treatment cycles and the left atrium area were adversely related to thrombus resolution. Nelles et al. performed a similar study with their retrospective single-centre registry analysis, including 78 patients with AF. In that patient cohort, a large proportion of participants were diagnosed with solid LAT despite being treated with NOAC (45% of patients) or VKA (41% of patients).[47] Their data show how thrombus resolution was achieved in almost half the enrolled patients during the mean follow-up time of 1 year, without a significant difference in efficacy between NOACs and VKAs. However, among those patients that responded to therapy with visualised thrombus resolution, there was a significantly shorter mean time to achieve that with NOACs versus VKA (81 versus 129 days; p=0.03).

Harada et al. previously showed how administering 300 mg of dabigatran (150 mg twice daily) in patients with LAAT and AF while on continuous NOAC therapy was effective in achieving thrombus resolution. However, this finding was obtained in a small sample size, and previous adherence to NOACs was not carefully evaluated.[48] Similar results were obtained in a small-sized study by Yilmaz et al., including 17 patients with AF and LAA thrombus who also completed baseline and follow-up TOE examinations after initiating or switching their anticoagulation regimen.[49] Patients in their study were treated with 300 mg dabigatran daily. Thrombus resolution was achieved in 87% of patients (7/8, all paroxysmal or persistent AF). At the same time, it was ineffective in only one patient with long-standing continuous AF. In another report, two patients with LAT resistant to rivaroxaban had thrombus resolution after starting dabigatran.[50] Dabigatran is the only OAC that serves as a direct thrombin inhibitor and a prodrug. In contrast, the others (rivaroxaban, apixaban and edoxaban) act as factor Xa inhibitors in their active forms, thus reflecting different mechanisms of action. They concluded that dabigatran given twice daily was more efficient than a factor Xa inhibitor given once daily at dissolving existing thrombi and preventing the creation of new ones.[50] The RIVA-TWICE prospective open-label study declared that when standard rivaroxaban therapy fails, rivaroxaban 15 mg twice daily appears as a safe therapeutic option and may dissolve LAA thrombus, with a resolution rate of LA/LAA thrombosis of 46.7%.[51]

A recent systematic review and meta-analysis comparing the use of NOAC versus warfarin for the treatment of LA thrombosis in patients with non-valvular AF showed that NOAC use was associated with a 2.2-fold increased probability of LAT resolution and this was not offset with higher risks of bleeding or stroke/transient ischaemic attack (TIA).[52] However, cautious interpretation of this analysis is advised since previous/current anticoagulation varied greatly across included trials. Some trials did not report previous anticoagulant exposure; some had all patients covered by NOACs or VKAs, while some enrolled patients were not previously treated with OACs.

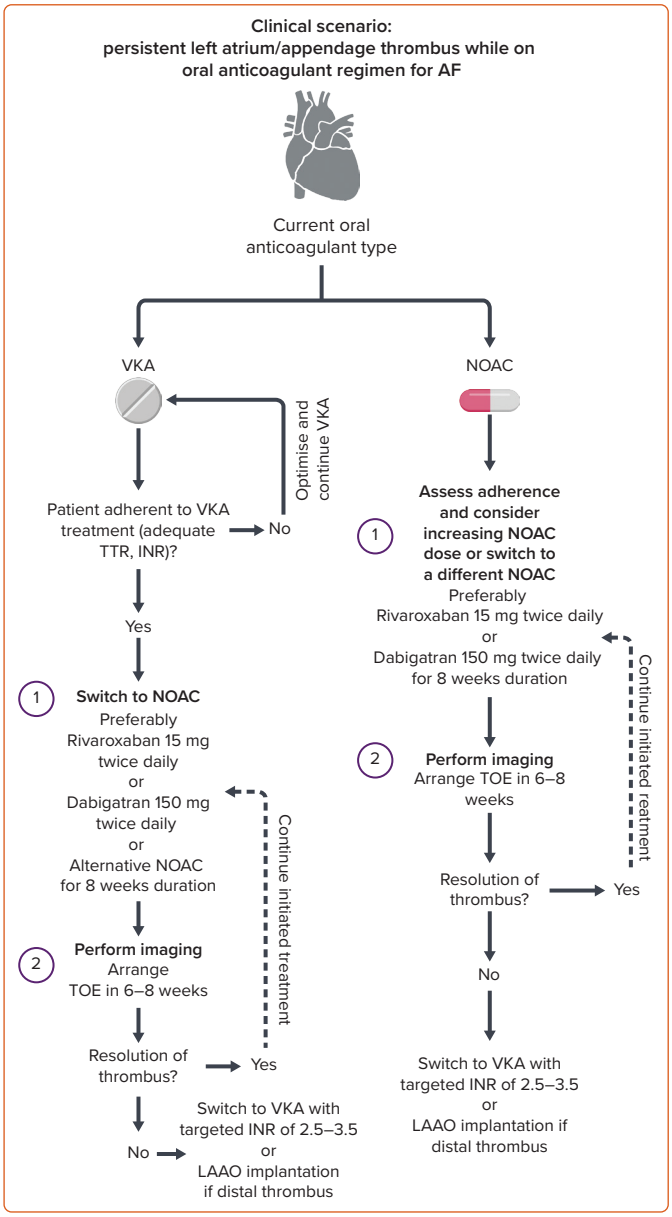
The formal approach and management strategy are laid out in the recent EHRA 2021 practical guide on using NOACs in patients with AF.[53] This document recommends that the management be individually tailored to each patient with AF with the persistent thrombus regardless of good adherence to NOAC treatment. Some general principles to consider are provided in this document – patients might be switched to a NOAC with a different mechanism of action (for example, switching from factor Xa

Figure 1: Risk Factors and Clinical Determinants of Left Atrial Appendage Thrombus in Patients With Non-valvular AF



HFrEF = heart failure with reduced ejection fraction; LA = left atrial; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist. Created with BioRender.com and reproduced with permission.

Figure 2: Treatment Pathway for Resistant Left Atrial/Left Atrial Appendage Thrombus



A proposed management pathway in the clinical scenario of persistent left atrial/appendage thrombus among patients already receiving full-dose continuous anticoagulant therapy for the purpose of stroke prevention in non-valvular AF. INR = international normalised ratio; LAAO = left atrial appendage occluder; NOAC = novel oral anticoagulant; TOE = transoesophageal echocardiography; TTR = time in therapeutic range; VKA = vitamin K antagonist. Source: Created with BioRender.com and reproduced with permission.

inhibitor to direct thrombin inhibitor or vice versa) or to VKA therapy with a customised INR target. Similarly, non-pharmacological alternative strategies such as LAA closure with dedicated devices might be considered in particular clinical scenarios. However, the authors clearly state the lack of prospective evidence in this setting.

Therefore, it becomes clear that all management decisions should be carefully balanced by estimating each individual patient's bleeding and thrombotic risks. Only a few options have been available regarding the results of LAA closure in patients with AF and LAA thrombus. A recent review that comprised 35% of patients whose LAA thrombosis was persistent and distally situated demonstrated that LAA occlusion (LAAO) was possible in these individuals.[54] The WATCHMAN device (Boston Scientific) requires the delivery sheath to be progressed into the LAA until its marker aligns with the LAA's ostial plane, which may increase the risk of distal contact and embolisation.[55] In this patient subgroup, the lobe and disc devices might be a better option for LAA closure.

Herein, we propose a management scheme to patients with persistent LA/LAA thrombus despite full-dose anticoagulation for non-valvular AF (*Figure 2*).

Adding Antiplatelet to Anticoagulation Drugs for the Pharmacological Resolution of Persistent Left Atrial Appendage Thrombus

To date, no randomised data or studies show the superiority or increased effectiveness of adding an antiplatelet agent to the existing or switched anticoagulant regimen for this indication. In a retrospective work by Kolakowski et al., it was suggested that keeping the same anticoagulant medication but adding an antiplatelet agent was associated with a numerically greater efficacy compared to several other strategies for LAA thrombus resolution (e.g. switch to an anticoagulant with a different mechanism, switch to an anticoagulant with a similar mechanism of action, switch to another anticoagulant with an added antiplatelet agent, adding a second anticoagulant drug or deliberate no change in treatment).[46] However, combining an OAC and antiplatelet failed to show a statistical advantage in efficacy over any other antithrombotic regimen. It can be concluded that the role of antiplatelet addition for this indication is highly limited and currently not supported by the evidence except in cases in which a patient has another indication, such as concomitant coronary artery disease.

Continuous Oral Anticoagulant Regimen Following Left Atrial Appendage Occlusion Device Implantation

While oral anticoagulation therapy is effective in mitigating thromboembolic risks in non-valvular AF, for some patients bleeding risks and nonadherence to therapy present important barriers in effective anticoagulation. For these patients, surgical and percutaneous LAAO devices are important non-pharmacological strategies to overcome the challenges of anticoagulant pharmacotherapy.[56] LAAO is also a feasible and safe therapeutic option for those patients that suffered a cerebrovascular event despite being on adequate anticoagulant treatment.[57]

The recent meta-analysis of observational data showed no difference in stroke, major bleeding, device-related thrombosis, and all-cause mortality rates in patients receiving antiplatelet versus anticoagulant agents following LAAO.[58]

However, whether patients after LAAO should still receive anticoagulants and, if yes, for how long and at what dose remains an open question in clinical practice.[59] The results of the real-world prospective study in which 41% of patients did not receive OAC while 59% received OAC after LAAO with the LARIAT device (SentreHEART Inc) showed that there was no difference between the two groups in relevant outcomes such as rates of ischaemic stroke/TIA, thromboembolic events, bleeding, life-threatening, disabling or significant events, and annual mortality rate.[60] Cepas-Guillen et al. recently conducted a study in which a low-dose strategy with apixaban (2.5 mg twice daily) was tested against single antiplatelet therapy (SAPT; low-dose aspirin 100 mg once daily) and DAPT (aspirin 100 mg + clopidogrel 75 mg once daily) in patients with non-valvular AF who underwent LAAO.[61] The authors concluded that a strategy with low-dose apixaban following LAAO might be a feasible and effective alternative to DAPT and SAPT concerning combined efficacy and safety

endpoints. However, this study was not randomised and enrolled a limited number of patients. In the ADRIFT trial, strategies of two doses of rivaroxaban were compared versus DAPT consisting of 75 mg aspirin and 75 mg clopidogrel in patients implanted with Amplatzer Amulet (Abbott) and WATCHMAN devices for LAAO.[62] This study showed that the circulating levels of prothrombin fragments 1 and 2 reflecting thrombin generation following the LAOO procedure were higher among patients treated with DAPT than 10 or 15 mg rivaroxaban. However, it remains unclear whether this effect can reduce adverse post-procedural events such as device-related thrombosis or other thromboembolic events. In line with this, Tjoe et al. showed, in a retrospective analysis of 213 patients, that use of DOAC with or without aspirin had similar safety and efficacy profile post-WATCHMAN device implantation when compared to warfarin and aspirin use.[63]

Furthermore, robust nationwide data on oral anticoagulation following LAAO became recently available from the LAAO Registry of the National Cardiovascular Data Registry that enrolled patients implanted with the WATCHMAN device in the US.[64] This extensive analysis of 31,994 patients who underwent successful LAAO showed that the most significant deviations from implantation protocol were observed in post-discharge antithrombotic medications. This analysis showed that the post-implantation discharge on warfarin or DOAC, compared to DOAC + aspirin or DAPT alone, was associated with a significant reduction in the composite endpoint of adverse outcomes.

Conclusion

Taken together, it seems that in case of LAA thrombus presence despite chronic anticoagulation treatment, most centres would practice switching to another anticoagulant drug with a different mechanism of action. In contrast, repeated imaging for LAA thrombus would be performed within 3–6 weeks in over 80% of cases. It is also evident that several essential questions in the scenario of LAA thrombus – despite apparently adherent chronic OAC treatment – remain unanswered. These are which anticoagulation drug should be selected in these cases, for how long treatment should be initiated, which dosing regimen should be selected and when should the follow-up imaging be arranged. As previously elaborated, relevant meta-analysis suggests increased efficacy with NOACs than warfarin, and there is limited clinical evidence that 300 mg of dabigatran might be particularly effective. However, these observations need to be confirmed in a prospective randomised fashion. In summary, it becomes evident that the optimal choice, dosing and duration of antithrombotic and anticoagulation treatment following LAAO is unclear and that high-quality large randomised trials adequately powered for relevant clinical outcomes are warranted. The role of continuous anticoagulant use following LAAO implantation would need to be prospectively validated by such studies. ❑

1. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;37:1591–602. https://doi.org/10.1093/eurheartj/ehw007; PMID: 26888184.
2. Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–64. https://doi.org/10.1016/s0002-9343(02)01236-6; PMID: 12401529.
3. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation meta-analysis. *Ann Intern Med* 1999;131:492–501. https://doi.org/10.7326/0003-4819-131-7-199910050-00003; PMID: 10507957.
4. Giugliano RP, Ruf CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104. https://doi.org/10.1056/NEJMoa1310907; PMID: 24251359.
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51. https://doi.org/10.1056/NEJMoa0905561; PMID: 19717844.
6. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92. https://doi.org/10.1056/NEJMoa1107039; PMID: 21870978.
7. Chen YY, Liu Q, Liu L, et al. Effect of metabolic syndrome on risk stratification for left atrial or left atrial appendage thrombus formation in Patients with nonvalvular atrial fibrillation. *Chin Med J (Engl)* 2016;129:2395–402. https://doi.org/10.4103/0366-6999.191744; PMID: 27748329.
8. Cohoon KP, McBane RD, Ammash N, et al. Relationship between body mass index and left atrial appendage thrombus in nonvalvular atrial fibrillation. *J Thromb Thrombolysis* 2016;41:613–8. https://doi.org/10.1007/s11239-015-1266-7; PMID: 26282111.
9. Ezekowitz MD, Pollack CV, Halperin JL, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J* 2018;39:2959–71. https://doi.org/10.1093/eurheartj/ehy148; PMID: 29659797.
10. Kitkungvan D, Nabi F, Ghosn MG, et al. Detection of LA and LAA thrombus by CMR in patients referred for pulmonary vein isolation. *JACC Cardiovasc Imaging* 2016;9:809–18. https://doi.org/10.1177/1747493018778713; PMID: 29786478.
11. Erickson M, Yadav H, Sneij E, et al. Incidence of left atrial appendage thrombus desthreeite three weeks of anticoagulation and the need for precardioversion echocardiography. *Ann Noninvasive Electrocardiol* 2022;27:e12989. https://doi.org/10.1111/anec.12989; PMID: 35802810.
12. Stoddard MF, Singh P, Dawn B, Longaker RA. Left atrial thrombus predicts transient ischemic attack in patients with atrial fibrillation. *Am Heart J* 2003;145:676–82. https://doi.org/10.1067/mhj.2003.91; PMID: 12679765.
13. Mügge A, Kühn H, Nikutta P, et al. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol* 1994;23:599–607. https://doi.org/10.1016/0735-1097(94)90743-9; PMID: 8113541.
14. Frenkel D, D'Amato SA, Al-Kazaz M, et al. Prevalence of left atrial thrombus detection by transesophageal echocardiography a comparison of continuous non–vitamin K antagonist oral anticoagulant versus warfarin therapy in patients undergoing catheter ablation for atrial fibrillation. *JACC Clin Electrophysiol* 2016;2:295–303. https://doi.org/10.1016/j.jacep.2016.01.004; PMID: 29766887.
15. Wu M, Gabriels J, Khan M, et al. Left atrial thrombus and dense spontaneous echocardiographic contrast in patients on continuous, direct oral anticoagulant therapy undergoing catheter ablation of atrial fibrillation: comparison of dabigatran, rivaroxaban, and apixaban. *Heart Rhythm* 2018;15:496–502. https://doi.org/10.1016/j.hrthm.2017.12.005; PMID: 29605015.
16. Yamaji K, Fujimoto S, Yutani C, et al. Is the site of thrombus formation in the left atrial appendage associated with the risk of cerebral embolism? *Cardiology* 2002;97:104–10. https://doi.org/10.1159/000057681; PMID: 11978958.
17. Angelini F, Bocchino PP, Peyracchia M, et al. Prevalence and predictors of left atrial thrombosis in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants. *Acta Cardiol* 2021. https://doi.org/10.1080/00015385.2021.2005307; PMID: 34821203; online ahead of press.
18. Bertaglia E, Anselmino M, Zorzi A, et al. NOACs and atrial fibrillation: incidence and predictors of left atrial thrombus in the real world. *Int J Cardiol* 2017;249:179–83. https://doi.org/10.1016/j.ijcard.2017.07.048; PMID: 29121724.
19. Durmaz E, Karpuz MH, Bilgehan K, et al. Left atrial thrombus in patients with atrial fibrillation and under oral anticoagulant therapy; 3-D transesophageal echocardiographic study. *Int J Cardiovasc Imaging* 2020;36:1097–103. https://doi.org/10.1007/s10554-020-01811-x; PMID: 32140812.
20. Springer A, Schleberger R, Oyen F, et al. Genetic and clinical predictors of left atrial thrombus: a Single Center case-control study. *Clin Appl Thromb Hemost* 2021;27:1-7. https://doi.org/10.1177/10760296211021171; PMID: 34184557.
21. Yao Y, sheng SM, et al. Elevated homocysteine increases the risk of left atrial/left atrial appendage thrombus in non-valvular atrial fibrillation with low CHA2DS2-Vasc score. *Europace* 2017;20:1093–8. https://doi.org/10.1093/europace/eux189; PMID: 28637244.
22. Karwowski J, Rekosz J, Mączyńska-Mazuruk R, et al. Left atrial appendage thrombus in patients with atrial fibrillation who underwent oral anticoagulation. *Cardiol J* 2022. https://doi.org/10.5603/CJ.a2022.0054; PMID: 35703043; online ahead of press.
23. Kapłon-Cieślicka A, Budnik M, Gawałko M, et al. Atrial fibrillation type and renal dysfunction as essential predictors of left atrial thrombus. *Heart* 2019;105:1310–5. https://doi.org/10.1136/heartjnl-2018-314492; PMID: 31040170.
24. Whiteside HL, Nagabandi A, Brown K, et al. Prevalence and clinical characteristics associated with left atrial thrombus detection: apixaban. *World J Cardiol* 2019;11:84–93. https://doi.org/10.4330/wjc.v11.i2.84; PMID: 30820278; PMCID: PMC6391620.
25. Anselmino M, Gili S, Castagno D, et al. Do left atrial appendage morphology and function help predict thromboembolic risk in atrial fibrillation? *J Cardiovasc Med (Hagerstown)* 2016;17:169–76. https://doi.org/10.2459/JCM.0000000000000305; PMID: 26556443.
26. Wang F, Zhu M, Wang X, et al. Predictive value of left atrial appendage lobes on left atrial thrombus or spontaneous echo contrast in patients with non-valvular atrial fibrillation. *BMC Cardiovasc Disord* 2018;18:153. https://doi.org/10.1186/s12872-018-0889-y; PMID: 30064363.
27. Yamamoto M, Seo Y, Kawamatsu N, et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging* 2014;7:337–43. https://doi.org/10.1161/CIRCIMAGING.113.001317; PMID: 24523417.
28. Du H, Bi K, Xu L, et al. Analysis of risk factors for thrombosis of the left atrium/left atrial appendage in patients with non-valvular atrial fibrillation. *Cardiovasc J Afr* 2021;32:116–22. https://doi.org/10.5830/CVJA-2019-071; PMID: 33950066.
29. Zuo K, Sun L, Yang X, et al. Correlation between cardiac rhythm, left atrial appendage flow velocity, and CHA2DS2-vasc score: study based on transesophageal echocardiography and 2-dimensional speckle tracking. *Clin Cardiol* 2017;40:120–5. https://doi.org/10.1002/clc.22639; PMID: 28075503.
30. Clark CB, Telles Garcia NA, Hackett Renner C, Ryan SM. Correlation of left atrial appendage ejection velocities with the CHADS2 and CHA2DS2-vasc scores. *Echocardiography* 2016;33:1195–201. https://doi.org/10.1111/echo.13228; PMID: 27060690.
31. Akoum N, Fernandez G, Wilson B, et al. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. *J CardioVasc Electrophysiol* 2013;24:1104–9. https://doi.org/10.1111/jce.12199; PMID: 23844972.
32. Watanabe A, Suzuki S, Kano H, et al. Left atrial remodeling assessed by transthoracic echocardiography predicts left

atrial appendage flow velocity in patients with paroxysmal atrial fibrillation. *Int Heart J* 2016;57:177–82. https://doi.org/10.1536/ihj.15-345; PMID: 26973273.
33. Bisbal F, Gómez-Pulido F, Cabanas-Grandío P, et al. Left atrial geometry improves risk prediction of thromboembolic events in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2016;27:804–10. https://doi.org/10.1111/jce.12978; PMID: 27027899.
34. Dudzińska-Szczerba K, Zalewska M, Niemiro W, et al. Association of left atrial sphericity with risk of stroke in patients with atrial fibrillation. Sub-analysis of the Assam study. *Cardiovasc Eng Technol* 2022;13:419–27. https://doi.org/10.1007/s13239-021-00587-y; PMID: 34750781.
35. Uziębło-Życzkowska B, Krzesiński P, Jurek A, et al. Left ventricular ejection fraction is associated with the risk of thrombus in the left atrial appendage in patients with atrial fibrillation. *Cardiovasc Ther* 2020;2020:3501749. https://doi.org/10.1155/2020/3501749; PMID: 32411299.
36. Kim MN, Kim SA, Choi JI il, et al. Improvement of predictive value for thromboembolic risk by incorporating left atrial functional parameters in the CHADS2 and CHA2DS2-vasc scores. *Int Heart J* 2015;56:286–92. https://doi.org/10.1536/ihj.14-380; PMID: 25912904.
37. Lu X, Chen T, Liu G, et al. Relations between left atrial appendage contrast retention and thromboembolic risk in patients with atrial fibrillation. *J Thromb Thrombolysis* 2022;53:191–201. https://doi.org/10.1007/s11239-021-02490-8; PMID: 34128199.
38. Lee WC, Fang CY, Chen YL, et al. Left atrial or left atrial appendage thrombus resolution after adjustment of oral anticoagulant treatment. *J Stroke Cerebrovasc Dis* 2019;28:90–6. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.015; PMID: 30301596.
39. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. *Hematology Am Soc Hematol Educ Program* 2018;2018:339–47. https://doi.org/10.1182/asheducation-2018.1.339; PMID: 30504330.
40. Ellis CR, Kanagasundram AN. Atrial fibrillation in heart failure left atrial appendage management. *Cardiol Clin* 2019;37:241–9. https://doi.org/10.1016/j.ccl.2019.01.009; PMID: 30926025.
41. Wybraniec MT, Mizia-Szubryt M, Cichoń M, et al. Heart failure and the risk of left atrial thrombus formation in patients with atrial fibrillation or atrial flutter. *ESC Heart Fail* 2022;9:4064–76. https://doi.org/10.1002/ehf2.14105; PMID: 36039813.
42. Merino JL, Lip GYH, Heidbuchel H, et al. Determinants of left atrium thrombi in scheduled cardioversion: an ENSURE-AF study analysis. *Europace* 2019;21:1633–8. https://doi.org/10.1093/europace/euz213; PMID: 31436835.
43. Noubiap JJ, Agbaedeng TA, Ndoadoumgue AL, et al. Atrial thrombus detection on transoesophageal echocardiography in patients with atrial fibrillation undergoing cardioversion or catheter ablation: a pooled analysis of rates and predictors. *J Cardiovasc Electrophysiol* 2021;32:2179–88. https://doi.org/10.1111/jce.15082; PMID: 33969568.
44. Kurzawski J, Janion-Sadowska A, Zandecki L, et al. Global peak left atrial longitudinal strain assessed by transthoracic echocardiography is a good predictor of left atrial appendage thrombus in patients in sinus rhythm with heart failure and very low ejection fraction – an observational study. *Cardiovasc Ultrasound* 2020;18:7. https://doi.org/10.1186/s12947-020-00188-0; PMID: 32061249.
45. Farkowski MM, Jubele K, Marín F, et al. Diagnosis and management of left atrial appendage thrombus in patients with atrial fibrillation undergoing cardioversion or percutaneous left atrial procedures: results of the European Heart Rhythm Association survey. *Europace* 2019;22:162–9. https://doi.org/10.1093/europace/euz257; PMID: 31501852.
46. Kołakowski K, Farkowski MM, Pytkowski M, et al. The comparative effectiveness and safety of different anticoagulation strategies for treatment of left atrial appendage thrombus in the setting of chronic anticoagulation for atrial fibrillation or flutter. *Cardiovasc Drugs Ther* 2023;37:159-68. https://doi.org/10.1007/s10557-021-07278-9; PMID: 34669102.
47. Nelles D, Lambers M, Schafigh M, et al. Clinical outcomes and thrombus resolution in patients with solid left atrial appendage thrombi: results of a single-center real-world registry. *Clin Res Cardiol* 2021;110:72–83. https://doi.org/10.1007/s00392-020-01651-8; PMID: 32307589.
48. Harada M, Koshikawa M, Motoike Y, et al. Left atrial appendage thrombus prior to atrial fibrillation ablation in the era of direct oral anticoagulants. *Circ J* 2018;82:2715–21. https://doi.org/10.1253/circj.CJ-18-0398; PMID: 30101809.
49. Yilmaz KC, Ciftci O, Ozin B, Muderrisoglu H. Anticoagulants in left atrial thrombus resolution. *Ann Med Res* 2020;27:1908–12. https://doi.org/10.5455/annalsmedres.2020.03.284.
50. Watanabe T, Shinoda Y, Ikeoka K, et al. Dabigatran therapy resulting in the resolution of Rivaroxaban-resistant left atrial appendage thrombi in patients with atrial fibrillation. *Intern Med* 2017;56:1977–80. https://doi.org/10.2169/internalmedicine.56.8508; PMID: 28768967.
51. Piotrowski R, Zaborska B, Pilichowska-Paszkiet E, et al. Rivaroxaban TWICE daily for lysis of thrombus in the left atrial appendage in patients with non-valvular atrial fibrillation: the RIVA-TWICE study. *Arch Med Sci AMS* 2019;16:289–96. https://doi.org/10.5114/aoms.2019.86616; PMID: 32190138.
52. Dong SJ, Luo CY, Xiao CL, et al. Efficacy and safety profile of novel oral anticoagulants in the treatment of left atrial thrombosis: a systematic review and meta-analysis. *Curr Ther Res Clin Exp* 2022;96:100670. https://doi.org/10.1016/j.curtheres.2022.100670; PMID: 35515958.
53. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;23:1612–76. https://doi.org/10.1093/europace/euab065; PMID: 33895845.
54. Sharma SP, Cheng J, Turagam MK, et al. Feasibility of left atrial appendage occlusion in left atrial appendage thrombus a systematic review. *JACC Clin Electrophysiol* 2020;6:414–24. https://doi.org/10.1016/j.jacep.2019.11.017; PMID: 32327075.
55. Jalal Z, Iriart X, Dinet ML, et al. Extending percutaneous left atrial appendage closure indications using the AMPLATZERTM cardiac plug device in patients with persistent left atrial appendage thrombus: the thrombus trapping technique. *Arch Cardiovasc Dis* 2016;109:659–66. https://doi.org/10.1016/j.acvd.2016.02.012; PMID: 27402154.
56. Collado FMS, von Buchwald CML, Anderson CK, et al. Left atrial appendage occlusion for stroke prevention in nonvalvular atrial fibrillation. *J Am Heart Assoc* 2021;10:e022274. https://doi.org/10.1161/JAHA.121.022274; PMID: 34668395.
57. Falasconi G, Gaspardone C, Godino C, et al. Left atrial appendage closure: a new strategy for cardioembolic events despite oral anticoagulation. *Panminerva Med* 2021. https://doi.org/10.23736/S0031-0808.21.04446-3; PMID: 34664480; epub ahead of press.
58. Osman M, Busu T, Osman K, et al. Short-term antiplatelet versus anticoagulant therapy after left atrial appendage occlusion a systematic review and meta-analysis. *JACC Clin Electrophysiol* 2020;6:494–506. https://doi.org/10.1016/j.jacep.2019.11.009; PMID: 32439033.
59. Chew DS, Piccini JP. Postprocedural antithrombotic therapy following left atrial appendage occlusion: no longer adrift in uncertainty? *Circ Cardiovasc Interv* 2020;13:e009534. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009534; PMID: 32674680.
60. Litwinowicz R, Filip G, Sobczyk D, et al. Long-term effect of anticoagulation following left atrial appendage occlusion with the LARIAT device in patients with nonvalvular atrial fibrillation: impact on thromboembolism, bleeding and mortality. Real-life data. *Postepy Kardiol Interwencyjnej* 2020;16:89–96. https://doi.org/10.5114/aic.2020.93916; PMID: 32368241.
61. Cepas-Guillen PL, Flores-Umanzor E, Regueiro A, et al. Low dose of direct oral anticoagulants after left atrial appendage occlusion. *J Cardiovasc Dev Dis* 2021;8:142. https://doi.org/10.3390/jcdd8110142; PMID: 34821695.
62. Duthoit G, Silvain J, Marijon E, et al. Reduced rivaroxaban dose versus dual antiplatelet therapy after left atrial appendage closure: ADRIFT a randomized pilot study. *Circ Cardiovasc Interv* 2020;13e008481. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008481; PMID: 32674675.
63. Tjoe B, Nguyen H, Mandava S, et al. Use of direct oral anticoagulation therapy following implantation of the Watchman left atrial appendage occlusion device. *Struct Hear* 2021;5:295–301. https://doi.org/10.1080/24748706.2021.1890286.
64. Freeman JV, Higgins AY, Wang Y, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol* 2022;79:1785–98. https://doi.org/10.1016/j.jacc.2022.02.047; PMID: 35512858.