



Case Study

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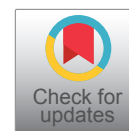
Left Atrial Appendage Thrombus Resolution with Clopidogrel after Apixaban Failure: A Case Series

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Abstract

This hypothesis-generating, case series reviews the evidence available for managing left atrial appendage thrombus in patients already on therapeutic anticoagulation with apixaban. Our six patient cases highlight the first documented evidence of complete, accelerated clot resolution upon the addition of P2Y12 inhibitor, clopidogrel, to current therapeutic doses of apixaban.

Keywords

Clopidogrel, apixaban, LAA thrombus

Abbreviations

LAA: Left atrial appendage; LAAT: Left atrial appendage thrombus; DOAC: Direct oral anticoagulant; TEE: Transesophageal echocardiography; ASCVD: Atherosclerotic cardiovascular disease; TAVR: Transcatheter aortic valve replacement; CVA: Cerebrovascular accident; Scr: Serum creatinine

Introduction

Nonvalvular atrial fibrillation increases the risk of atrial thrombi formation, particularly in the left atrial appendage (LAA), which predisposes patients to ischemic stroke [1-3]. Oral anticoagulation, with a vitamin K antagonist (VKA) or direct oral anticoagulant (DOAC), is effective at decreasing ischemic stroke and systemic embolism, however treatment of a LAA thrombus shows resolution rates ranging from 50-90% despite therapeutic anticoagulation [4-10]. Strategies to treat a LAA thrombus while on therapeutic anticoagulation are limited. Case reports are documented showing LAA thrombi present in patients on warfarin with subtherapeutic INRs that subsequently resolve upon improving the time in therapeutic range or switching to a DOAC [11-13]. DOACs, which are being used more widespread for stroke prevention in atrial fibrillation, are documented to be as effective as warfarin in resolving LAA thrombi [9,10,14,15]. However, there is limited evidence describing how to treat LAA thrombi in the setting of therapeutic DOAC therapy. Limited reports suggest effective options include switching the patient to another DOAC or warfarin, or increasing an inappropriately low DOAC dose [11,16,17]. Nevertheless, resolution takes time, up to 13-16 weeks, and several thrombi remain unresolved [10,18].

To our knowledge, this is the first documented case series of complete, accelerated LAA thrombi resolution with the addition of P2Y12 inhibitor therapy in patients on therapeutic doses of a DOAC, specifically, apixaban.

Case 1

An 89-year-old male, 81.9 kg with persistent atrial fibrillation (CHA₂DS₂-VASc score 4), heart failure with preserved ejection fraction, severe aortic stenosis, ASCVD, hypertension and hyperlipidemia presented to the hospital for a transfemoral transcatheter aortic valve replacement (TAVR). Echocardiography showed the patient had a LAA thrombus despite adherence to warfarin therapy. Patient's

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INR two weeks prior was reported as subtherapeutic at 1.8. After his TAVR, prior to discharge, he was switched to apixaban 2.5 mg twice daily, dosed accordingly based on his age, weight and serum creatinine (Scr) of 2.3 mg/dL. He was also discharged on aspirin 81 mg, lisinopril, furosemide, lovastatin, fenofibrate, amlodipine, tamsulosin, omeprazole, and finasteride. The patient presented 6 weeks post-TAVR for a TEE for evaluation of a Watchman device. TEE showed the presence of a LAA thrombus, despite being adherent to apixaban therapy for 41 days. The patient was started on clopidogrel 75 mg daily, in addition to apixaban. A follow up TEE 15 days after clopidogrel initiation revealed the resolution of the LAA thrombus.

Case 2

An 88-year-old male, 97.2 kg, with persistent atrial fibrillation (CHA₂DS₂VASc 5), hypertension, hyperlipidemia, ASCVD and history of stroke presented for evaluation of a Watchman device. A CT with contrast showed a LAA thrombus, subsequently confirmed by TEE, despite being on warfarin therapy. INR was subtherapeutic at 1.8, although the patient reported that his INR is typically between 2 and 2.5. With the discovery of the LAA thrombus, the patient was transitioned to apixaban 5 mg twice daily, dosed appropriately based on his age, weight and Scr of 1.33 mg/dL. In addition, he was on carvedilol, furosemide, hydralazine, KCl, atorvastatin, carbamazepine and levothyroxine. The patient was adherent to the apixaban 5 mg twice daily regimen and presented 10 days later for a TEE. The LAA clot was still present, therefore, clopidogrel 75 mg po daily was added to the regimen in efforts to dissolve the LAA thrombus. A follow up TEE 21 days after clopidogrel initiation revealed complete resolution of the thrombus.

Case 3

An 89-year-old male, 81.8 kg, with persistent atrial fibrillation (CHA₂DS₂VASc 5), heart failure with preserved ejection fraction, significant lung disease requiring home oxygen, hypertension, history of transient cerebral ischemic attack, bradycardia with pacemaker placement and chronic kidney disease presented for evaluation of a Watchman device. CT scan showed a LAA thrombus, which was later confirmed by TEE, despite apixaban therapy. The patient had been taking apixaban 2.5 mg po twice daily for 4 years, which was appropriate based on his age, weight and Scr of 2.0 mg/dL. Additional medications included furosemide, sacubitril/valsartan, metoprolol succinate, atorvastatin, tramadol, omeprazole, duloxetine and ropinirole. When the LAA thrombus was seen on CT, the apixaban dose was increased to 5 mg twice daily. One week later, the LAA thrombus was still present and unchanged on repeat TEE and therefore the patient was started on aspirin 81 mg and clopidogrel 75 mg daily in addition to the apixaban 5 mg twice daily. A follow up TEE 17 days later revealed resolution of the thrombus.

Case 4

An 84-year-old female, 64.5 kg, with paroxysmal atrial fibrillation (CHA₂DS₂VASc 4), hypertension and pulmonary hypertension presented for evaluation of a Watchman device.

She reported adherence to apixaban 2.5 mg twice daily for two years, which was a subtherapeutic dose given her age, weight and Scr of 1.1 mg/dL. She was also on pravastatin, bumetanide, lisinopril, metoprolol succinate, oxybutynin, quetiapine, and levothyroxine. On presentation to the office, CT scan showed a LAA thrombus. The patient was started on clopidogrel 75 mg daily in addition to apixaban. Follow up TEE 32 days later revealed complete resolution of the LAA thrombus.

Case 5

A 68-year-old male, 75 kg, with persistent atrial fibrillation (CHA₂DS₂VASc 5), history of CVA, hypertension, hyperlipidemia, heart failure with preserved ejection fraction, ASCVD, and tricuspid valve regurgitation presented for evaluation for a Watchman device. The patient was anticoagulated with apixaban 5 mg twice daily for two years, which was appropriate based on his age, weight and Scr of 0.81 mg/dL. He was also on atenolol, atorvastatin, esomeprazole, allopurinol, gabapentin, dutasteride, alfuzosin and milk thistle. A CT scan showed a potential LAA thrombus which was subsequently confirmed by TEE. At that point, clopidogrel 75 mg daily was added to the patient's medication regimen. A TEE 25 days later showed resolution of the LAA thrombus.

Case 6

A 72-year-old male, 105 kg, with permanent atrial fibrillation (CHA₂DS₂VASc 4), nonrheumatic mitral valve insufficiency with mitral tissue valve replacement, cardiomyopathy, hypertension, hyperlipidemia, ASCVD and pacemaker placement presented for evaluation of a Watchman device. The patient was switched from warfarin to apixaban 5 mg twice daily 9 months prior, which was an appropriate dose based on his age, weight and Scr 1.49 mg/dL. In addition to apixaban, he was also on aspirin 81 mg, bumetanide, clonidine, lisinopril, metoprolol succinate, pravastatin, finasteride, tamsulosin, sertraline, famotidine and ferrous sulfate. A CT showed LAA thrombus which was confirmed with a TEE. The patient stopped the aspirin and started clopidogrel 75 mg daily in addition to apixaban. A repeat TEE 18 days later revealed resolution of LAA thrombus.

Discussion

The presence of LAA thrombi in patients with atrial fibrillation is concerning as this is where over 90% of cardiac emboli originate in nonvalvular atrial fibrillation [1-3]. Treatment for the resolution of LAA thrombi is imperative in reducing the risk of ischemic stroke. Studies have observed 10-30% of atrial fibrillation patients not on anticoagulation have LAA thrombi present by TEE [19-23]. Oral anticoagulation with either warfarin or a DOAC is considered standard of care for ischemic stroke prevention in atrial fibrillation, however LAA thrombus may still exist despite therapeutic anticoagulation. In addition, when identified, LAA thrombus resolution rates range from 50-90% despite therapeutic anticoagulation with warfarin [4-6]. Studies of patients with atrial fibrillation detected LAA thrombi by TEE in 7-9% despite being on therapeutic warfarin with an INR 2-3 [13,24]. Those

rates of LAA thrombi further increase, in fact almost double, when patients have subtherapeutic INRs of < 2.0.(13,25)

DOAC therapy for LAA thrombi resolution has been supported by several case reports in the past couple of years [12,25-27]. Scarano M, et al. and Li Y, et al. both describe case reports of rivaroxaban utilized for resolution of LAA thrombus, showing complete resolution by 3 months and 5 weeks, respectively, after transitioning therapy to rivaroxaban [12,28]. In 2016, the X-TRA trial was the first prospective, multicenter study looking at the efficacy of rivaroxaban in resolving LAA thrombi in warfarin naïve or subtherapeutic warfarin patients [9]. The study looked at the resolution of LAA thrombi on TEE in patients after rivaroxaban therapy. From the 53 patients with LAA thrombi on initial TEE, 95% were Eastern European and the median CHA₂DS₂VASc score was 4. 81.7% of patients received the 20 mg dose and 18.3% received the 15 mg dose based on renal function. Adherence was accounted for and shown to be 100%. After 6-8 weeks of rivaroxaban therapy, follow up TEE showed thrombus resolution was 41.5% (95% CI 28.1%-55.9%) and the rate of resolved or reduced thrombus was 60.4% (95% CI 46.0% - 73.6%). Thrombus resolution tended to be observed in older patients and those with a lower CHA₂DS₂VASc. The retrospective, observational registry, CLOT-AF, indicated resolution rates in patients on rivaroxaban to be 62.5% [9]. This number suggests that a proportion of patients will have thrombus resolution or reduction with factor Xa inhibitor, rivaroxaban. Yet as documented with warfarin, a significant number of patients will not have thrombus resolution despite being adherent to DOAC therapy. In fact, studies are indicating that the DOAC resolution rates are similar to those seen with warfarin. A real world observational study reported a 60% LAA thrombus resolution rate in atrial fibrillation patients who were deemed to be appropriately anticoagulated [10]. Authors found no difference in the type of oral anticoagulant that was selected. Additionally, a recent retrospective study of 388 atrial fibrillation patients found that after 4 weeks of DOAC therapy, there was no difference in the prevalence of LAA thrombi between DOAC and warfarin therapy (4.4% vs. 2.9%, $p = 0.45$) [15]. This was similar to findings from another trial assessing the prevalence of LAA thrombi in 559 Japanese patients with nonvalvular atrial fibrillation, which found no difference in LAA thrombi present on TEE after 3 weeks of therapy with a DOAC or warfarin (2.6% vs. 2.8%, $p = 0.86$) [14].

In this report, we describe 6 cases of patients with LAA thrombi despite oral therapeutic anticoagulation with factor Xa inhibitor, apixaban. Several case reports document successful LAA thrombus resolution in 2-8 weeks after initiating apixaban therapy [7,26,27]. However, all of our patients had LAA thrombus found by TEE or CT after adherence to apixaban. A multivariate analysis showed that an elevated BNP ≥ 173 pg/mL was the only independent predictor of LAA thrombi.(14) Other predictors of LAA thrombi described in the literature includes a higher CHA₂DS₂VASc score, decreased left atrial volume changes and the presence of spontaneous echocardiographic contrast. (13) Previous studies suggest that a larger left atrial dimension, lower LVEF and LV hypertrophy are also associated with the formation of LAA thrombi

[29,30]. All six of our patients had elevated CHA₂DS₂VASc scores of 4 or 5, perhaps predisposing these patients to a higher risk of developing a LAA thrombus, despite therapeutic anticoagulation.

In determining reasons for apixaban failure in preventing LAA thrombus in our 6 patients, we would be remiss if we did not consider the medication dose, medication adherence and medication interactions.

Three of our six patients were on apixaban 2.5 mg twice daily, whereas three patients were on the 5 mg twice daily dose. All doses were appropriate based on FDA approved package labelling, with the exception of one patient (case #5) that was put on the lower dose despite not meeting the 2 out of 3 criteria. Evidence has demonstrated that empirically reducing the dose of apixaban without meeting the labelled criteria leads to a significant increased risk of stroke [31]. In this one case, it does raise the question of overall efficacy and safety with the use of a reduced dose of apixaban that was not clinically studied.

Medication adherence is a huge determinant of efficacy, particularly since the DOAC half-lives are much shorter than warfarin. One in five patients in the stroke prevention in nonvalvular atrial fibrillation randomized controlled trials discontinued the DOAC therapy during follow up, leaving them unprotected from events [32]. Recent real-world registries demonstrate that nearly 40% of patients at risk of ischemic stroke do not receive any oral anticoagulation due to contraindications, bleeding or patient/provider preferences [32,33]. In this case series, all 6 of our patients reported adherence to the medications and refill schedules confirmed this.

Medication interactions can affect the serum drug concentration of the DOACs. In particular, with factor Xa inhibitors, such as apixaban, stimulation or inhibition of P-glycoprotein or CYP3A4 enzymes, can increase or decrease apixaban plasma levels. Apixaban plasma levels may be reduced by up to 50% when given in combination with strong P-gp or CYP3A4 inducers, such as carbamazepine, phenytoin, rifampin or St. John's wort. Patient case #2 was on concomitant carbamazepine therapy, which may have resulted in a subtherapeutic concentration of apixaban, potentially leading to inefficacy in preventing LAA thrombus. However, none of the other patients had medication interactions present that would result in a subtherapeutic serum apixaban concentration. Apixaban drug levels to confirm were not received based on limited availability. Only 2 of the 6 patients were on concomitant low dose aspirin therapy at baseline.

In evaluating our case series, we also wanted to ensure that our patients were receiving therapeutic anticoagulation with apixaban for an adequate amount of time before determining that it was not effective in preventing the LAA thrombus. Typically, the resolution of LAA thrombi is expected to occur within 3 to 4 weeks of therapeutic anticoagulation therapy, as current guidelines recommend VKA therapy or DOAC for 3 weeks upon detection of a LAA thrombus in atrial fibrillation patients [34]. Many of the studies discussed here re-image

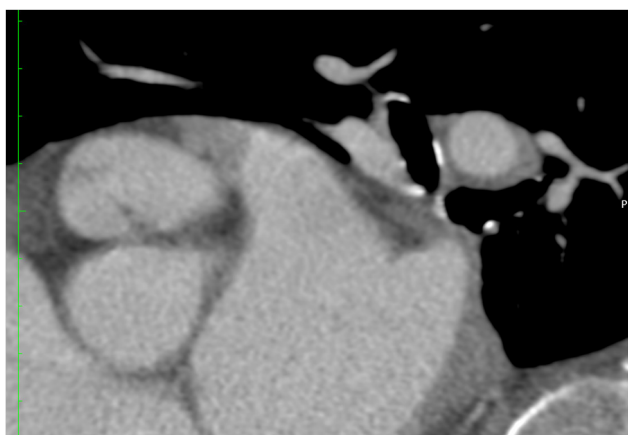


Figure 1: Case 4 Thrombus noted in LAA on delayed imaging of CT scan while on apixaban 2.5 mg twice daily.

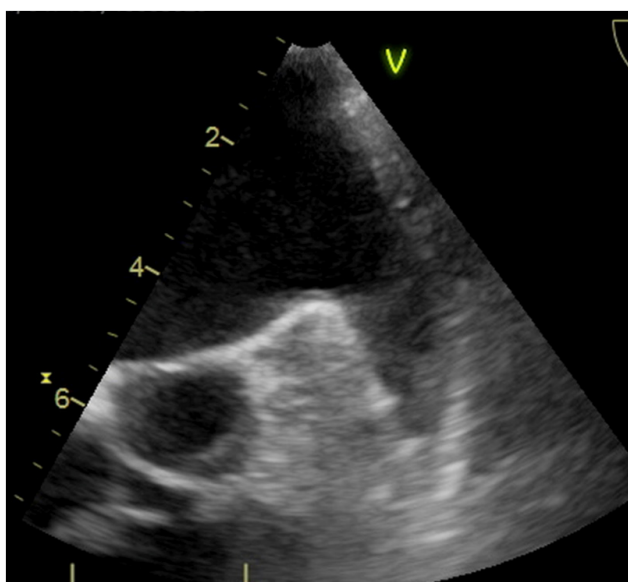


Figure 2: Case 4 Resolution of LAA thrombus 32 days after adding clopidogrel 75 mg daily to apixaban 2.5 mg twice daily.

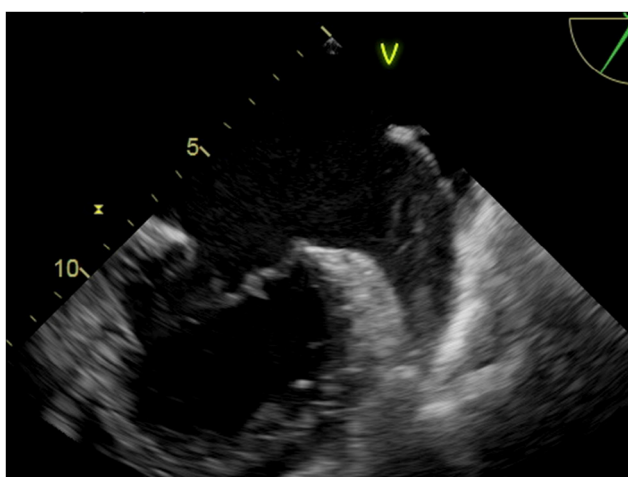


Figure 3: Case 5 LAA thrombus confirmed on TEE while on apixaban 5 mg twice daily.

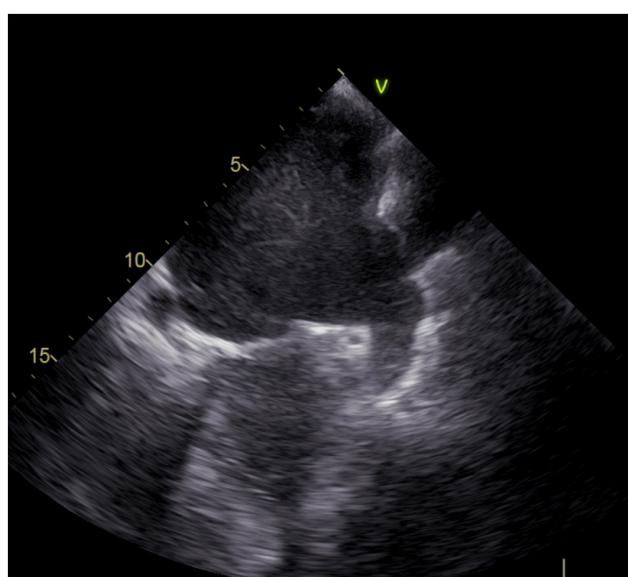


Figure 4: Case 5 Resolution of LAA thrombus 25 days after adding clopidogrel 75 mg daily to apixaban 5 mg twice daily.

patients for LAA thrombi after 3 to 4 weeks of anticoagulation. A study by Collins et al. showed 89% resolution of LAA thrombi in 18 patients with atrial fibrillation after 4 weeks of warfarin therapy [4]. One case report described a patient with atrial fibrillation and a large LAA thrombus on TEE who was started on rivaroxaban 20 mg daily and showed relevantly decreased thrombus size at 3 weeks and complete resolution after 5 weeks of rivaroxaban therapy [28]. In addition, other reports note the resolution of LAA thrombi prior to 3 to 4 weeks of therapy. A case report by Kawakami et al. demonstrated resolution after only 16 days of apixaban therapy [26]. In our series, patient case 1 was on apixaban therapy for about 6 weeks (41 days), patient case 6 for 9 months and patient cases 3, 4 and 5 were on apixaban for several years, which suggests adequate time for thrombi resolution. However, patient case 2, was on apixaban therapy for just 10 days prior to repeat TEE, which showed that the LAA thrombus remained present. It is unknown if a longer duration of therapy would have resulted in thrombus resolution, however, in this case it was not clinically feasible to wait for an extended period of time.

Understanding that LAA thrombi still exists despite adequate oral anticoagulation, the question remains on how to optimally treat patients with a LAA thrombi despite being adherent to an oral anticoagulant regimen, particularly a DOAC. We describe here 6 patient cases of LAA thrombi present despite oral anticoagulation with factor Xa inhibitor, apixaban, that resolved within 2 to 4 weeks after adding a P2Y12 inhibitor, clopidogrel, to the regimen. To our knowledge, this is the first report to demonstrate efficacy of this anticoagulant- antiplatelet combination in resolving a LAA thrombi observed while a patient was therapeutically anticoagulated with a direct oral anticoagulant. Documented strategies to treat LAA thrombi described from a real world study, included increasing the DOAC dose from an inappropriately low dose, maintaining the same DOAC and dose, or switching to warfarin [11]. Another option is to

Table 1: Demonstrates effective LAA thrombus resolution.

Case	Pt Age (years)	Gender	CHA ₂ DS ₂ VASc score	Med at time of LAAT discovery	Days to TEE resolution s/p clopidogrel
1	89	M	4	Warfarin, then apixaban	15
2	88	M	5	Warfarin, then apixaban	21
3	89	M	5	Apixaban	17
4	84	F	4	Apixaban	32
5	68	M	5	Apixaban	25
6	72	M	4	Apixaban	18

change the DOAC agent to one of an opposite mechanism. In a case report described by Koyama, et al., a 78-year-old male with atrial fibrillation, CHA₂DS₂VASc 3, was on dabigatran 110 mg po BID for stroke prevention [17]. The patient suffered a cerebral infarction and a TEE showed a large LAA thrombus. The patient was switched from dabigatran to apixaban 5 mg twice daily. Follow up TEE on day 7, showed no change in the size of LAA thrombus. On day 24, a reduction in thrombus size was shown on TEE and on day 56 of apixaban therapy, TEE showed complete resolution. A report by Watanabe, et al. described 2 cases in Japan that demonstrated the efficacy of dabigatran in resolving pre-existing LAA thrombi refractory to rivaroxaban [16]. Two patients, both on rivaroxaban for more than 2 years, were switched to dabigatran therapy after TEE discovered LAA thrombi. Resolution of the LAA thrombi was observed by TEE after 6 weeks in one patient and after 12 months for the second patient. The author supports the direct thrombin inhibitor, dabigatran, use for LAA thrombi as it not only inhibits both clot bound thrombin and soluble thrombin, but it also reduces thrombin-mediated activation of platelets. Its antiplatelet effects may also be associated with the authors findings that dabigatran is more effective in reduction of left atrial spontaneous echo contrast than warfarin. Perhaps targeting antiplatelet activity in LAA thrombi is a reasonable approach in those patients that fail anticoagulant therapy.

In this case series, we added antiplatelet effects to the factor Xa inhibitor using P2Y₁₂ inhibitor, clopidogrel. To our knowledge, this is the first study that demonstrates effective LAA thrombus resolution with the addition of a P2Y₁₂ inhibitor (Table 1). There is no published evidence of clopidogrel exhibiting a role in clot resolution. A study by Reiner et al. examined the use of direct P2Y₁₂ inhibitor ticagrelor in reducing the expression and activity of tissue factor and plasminogen activator inhibitor-1 (PAI-1), which may lead to the a lower level of thrombogenicity in the left atrial appendage [35]. The data found that ticagrelor, but not the active metabolite of clopidogrel, did in fact reduce the expression and activity of tumor necrosis factor-alpha (TNF-alpha) and PAI-1 in endocardial cells, suggesting a possible local antithrombotic effect of ticagrelor at a cellular level.

Conclusion

The presence of LAA thrombi in patients with nonvalvular atrial fibrillation may predispose patients to ischemic stroke, therefore resolution is imperative. DOACs appear to be an option to resolve LAA thrombi, however, often many LAA thrombi go unresolved despite appropriate anticoagulation. There are no clear guidelines on how to treat a patient on a

therapeutic DOAC that has the presence of a LAA thrombus. This report describes 6 patients that presented with LAA thrombus while on therapeutic anticoagulation with apixaban. We provide evidence that the addition of clopidogrel to the apixaban regimen led to quick thrombus resolution. Although further studies are needed, this evidence provides a new potential treatment option when a LAA thrombus is discovered despite adherence to DOAC therapy.

Learning Objectives

1. Describe the incidence and management of patients with LAA thrombi despite anticoagulation.
2. To examine P2Y₁₂ inhibitors as potential treatment options for patients with LAA thrombi despite anticoagulation with a DOAC.

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NA.

Conflict of Interest Disclosure

None for authors.

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