

Anticoagulation Management After Watchman Implantation

Current indications for antiplatelet agents and NOACs after Watchman implantation.

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Left atrial appendage (LAA) occlusion is increasingly being recognized as a valid nonpharmacologic therapy for stroke prevention in high-risk patients with nonvalvular atrial fibrillation (AF), especially in cases when long-term oral anticoagulation therapy (OAT) is contraindicated. Currently, the European Society of Cardiology guidelines for the management of AF recommend that LAA closure may be considered in patients at high risk for stroke and contraindications to long-term OAT (class IIb, level of evidence B).¹ The US Food and Drug Administration approved the Watchman device (Boston Scientific Corporation) in March 2015 for patients with nonvalvular AF who have a high risk of stroke and when there is an appropriate rationale to seek a nonpharmacologic alternative to warfarin.

After LAA closure with the Watchman device, thrombosis may appear on the surface of the device. The implantation of thrombogenic devices in patients with nonvalvular AF who are at high risk of thrombosis in the left atrium requires antithrombotic therapy to prevent on-device thrombus formation (Figure 1). Ideally, antithrombotic therapy should be pursued until complete occluder endothelialization occurs. Based on the post-implantation treatment protocols from the PROTECT AF and PREVAIL trials, the vast majority of Watchman implantations described in the literature were accompanied by warfarin anticoagulation for 45 days, followed by dual antiplatelet therapy (DAPT) for 6 months post-procedure and aspirin thereafter.

In a recent review, the rate of device-associated thrombosis (DAT) after LAA occlusion with Watchman was 3.4%.² Although most patients diagnosed with DAT are asymptomatic at the time of diagnosis, DAT can be associated with thromboembolic events (mostly neurologic). Moreover, in cases of DAT, intensification

of antithrombotic therapy was required to resolve the thrombus, which may increase the risk of a bleeding complication. Therefore, antithrombotic treatment after LAA occlusion is currently recommended. Predisposing factors for development of DAT are multifactorial and include patient characteristics, echocardiographic findings, procedural results, and device-related factors. Further studies are needed to evaluate the clinical impact of these predisposing factors.

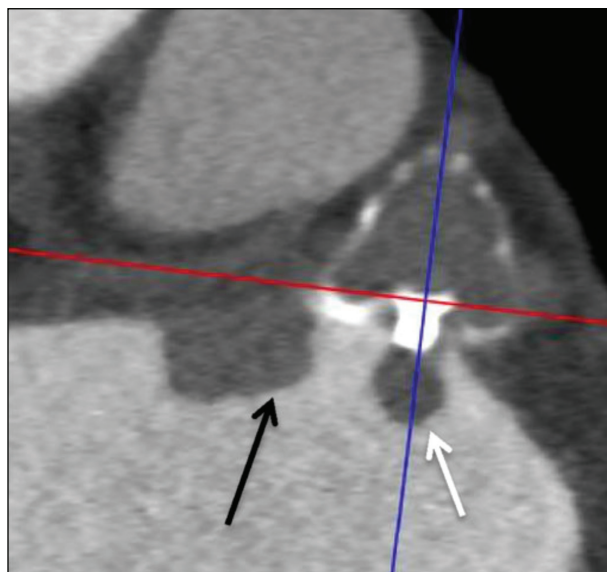


Figure 1. Contrast-enhanced CT images revealing an atrial-side device thrombus on a Watchman device at the fabric insert (white arrow) and adjacent to the device (black arrow). Reprinted from Saw J, Fahmy P, DeJong P, et al. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. *Eur Heart J Cardiovasc Imaging*. 2015;16:1198–1206, by permission of Oxford University Press.

Currently, the optimal antithrombotic regimen and its duration after Watchman implantation is still under debate and might be patient-specific. Anticoagulation remains the standard therapy in patients with low bleeding risk, whereas the use of antiplatelet agents may be indicated in some clinical settings when the risk of thromboembolism is balanced by the risk of bleeding. The role of non-vitamin K antagonist oral anticoagulants (NOACs) has yet to be determined.

USE OF ANTIPLATELET AGENTS AFTER WATCHMAN IMPLANTATION

Anticoagulation represents the most potent therapy after LAA occlusion to prevent thrombus formation (Figure 2). It is the therapy of choice for thromboembolism prevention in AF and has proven to be effective for treating DAT. In the largest randomized controlled trials comparing either LAA closure with the Watchman device or warfarin therapy in patients eligible for long-term OAT (the PROTECT AF and PREVAIL studies^{3,4}), it was recommended to give aspirin (81–325 mg) indefinitely with warfarin for 45 days. Warfarin was switched to clopidogrel (75 mg) after an absence of

device-related thrombus and significant peridevice leak (jet width \leq 5 mm) on control transesophageal echocardiography (TEE). Clopidogrel was continued for up to 6 months postprocedure. The rate of DAT was 4.2% in PROTECT AF and bleeding complications occurred in six patients in the first 45 days, translating to an estimated annual bleeding rate of 10.5%.⁵ However, compared to the warfarin treatment group, LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued.⁶

In real-world conditions, many patients treated with LAA closure are not eligible for long-term OAT. A European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions (EHRA/EAPCI) expert consensus statement⁷ on catheter-based LAA occlusion recommended an antithrombotic regimen based on the bleeding risk profile in patients treated with Watchman. Thus, when Watchman is implanted in patients with a high bleeding risk, the authors recommend treatment with clopidogrel for 1 to 6 months and aspirin indefinitely (Figure 3). The safety of antiplatelet treatment was initially derived from animal studies that analyzed endothelialization of cardiac devices,⁸ from

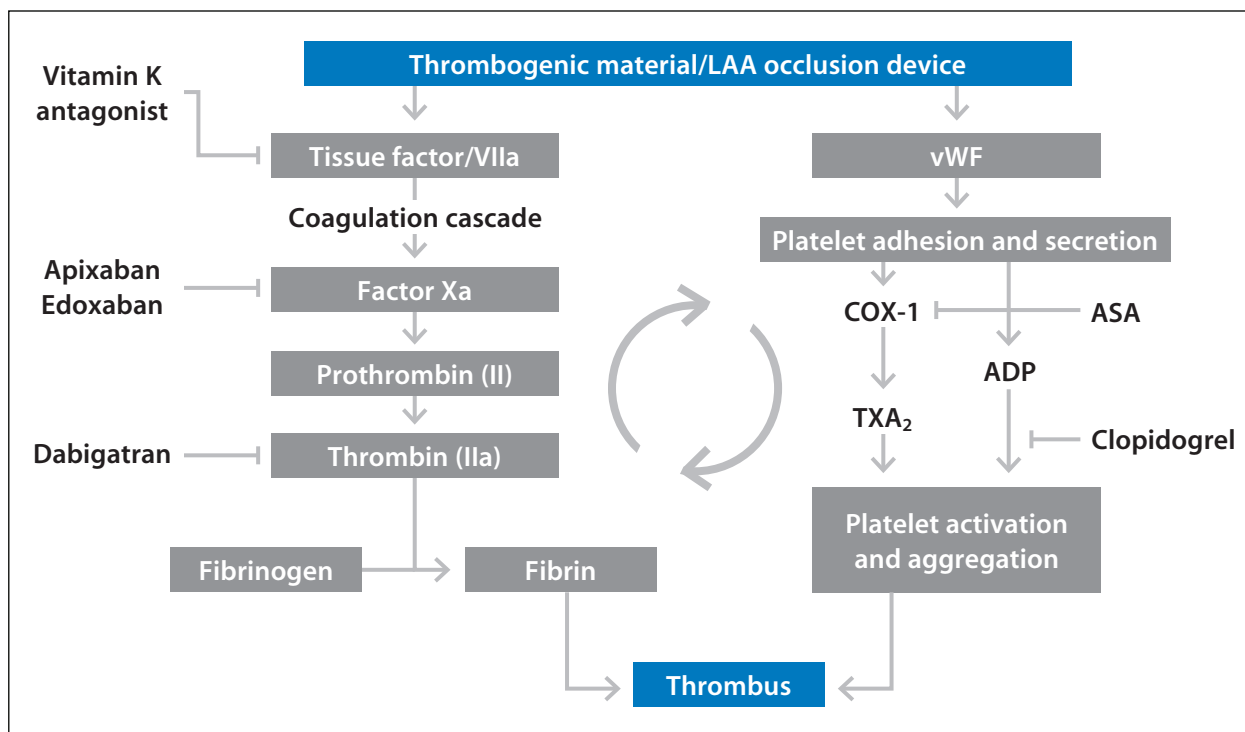


Figure 2. Pathophysiology of atherothrombosis and therapeutic targets. ADP, adenosine diphosphate; ASA, aspirin; COX-1, cyclooxygenase; TXA₂, thromboxane A₂; vWF, von Willebrand factor. Adapted from Shivu GN, Ossei-Gerning N. Rivaroxaban in patients with a recent acute coronary syndrome event: integration of trial findings into clinical practice. *Vasc Health Risk Manag.* 2014;10:291–302 and Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol.* 2015;12:30–47.

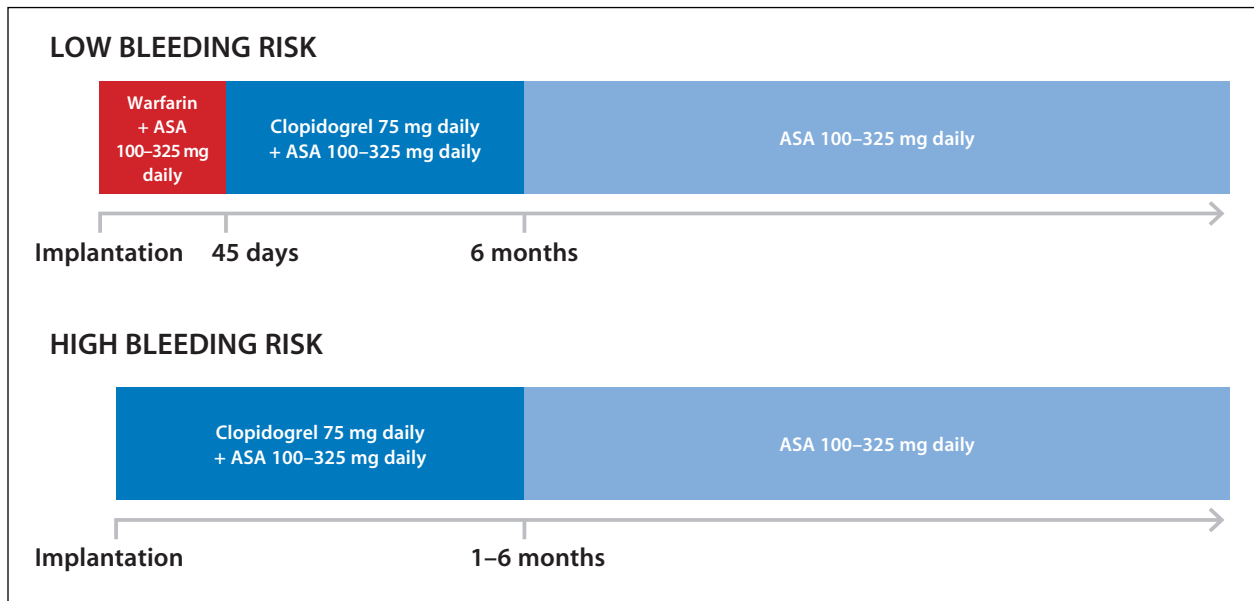


Figure 3. Timeline of antithrombotic treatment after LAA occlusion with the Watchman device based on bleeding risk as recommended by the EHRA/EAPCI consensus statement. ASA, aspirin. Adapted from Meier B, Blaauw Y, Khattab AA, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *EuroIntervention*. 2015;10:1109–1125 and Price MJ, Reddy VY, Valderrabano M, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the Watchman randomized trial experience. *JACC Cardiovasc Interv*. 2015;8:1925–1932.

previous experience with the PLAATO device,⁹ and from current practice after percutaneous patent foramen ovale or atrial septal defect closure device implantation.¹⁰

In the EWOLUTION registry, which reflects real-world results after Watchman implantation, 62% of patients were deemed unsuitable for OAT by their physician due to bleeding history or high bleeding risk, comorbidities, or an inability to adhere to OAT.¹¹ In this registry, after device implantation, as many as 59% of patients were on DAPT, and 27% of patients were on OAT. Subgroup analysis of serious adverse events through 7 days did not show any difference between patients who were OAT eligible or ineligible (5.2% vs 3.4%; $P = .18$) or between patients on OAT after implantation or those who were not (4.4% vs 4%; $P = .807$). However, it will be important to assess mid- and long-term results because DAT and its related complications are usually diagnosed later after the implantation (mean delay of 45 days from implantation to diagnosis).

In the ASAP study, 150 patients who were deemed ineligible for OAT were placed on 6 months of clopidogrel or ticlopidine and lifelong aspirin after Watchman implantation and showed favorable safety results as compared to PROTECT AF data (ischemic stroke rate of 1.7% vs 2.2%, respectively).¹² The rate of DAT was 4%, and there were five bleeding complications during the first 6 months, translating to an estimated annual bleeding rate of 6.6%. In a trial studying the Amplatzer cardiac plug (ACP; Abbott

Vascular), it was common practice to treat patients with DAPT after device implantation as follows: aspirin 80 to 100 mg and clopidogrel 75 mg daily for 1 to 3 months and then only aspirin 80 to 100 mg daily for at least another 3 months. With this therapeutic regimen, the reported rate of DAT in the ACP multicenter study was 4.4%.¹³ In a recent smaller study, 104 patients implanted with the ACP were treated with aspirin monotherapy and demonstrated a low rate of DAT or stroke postimplantation after a median follow-up of 2.3 years.¹⁴ Further studies will have to evaluate the need for long-term aspirin therapy.

The use of antiplatelet therapy after Watchman implantation appears to be a good alternative in patients with a high bleeding risk. This treatment should ideally be evaluated in randomized trials. A large trial is currently ongoing to evaluate the safety and efficacy of antiplatelet therapy after LAA closure in patients contraindicated for long-term OAT (ASAP TOO, NCT02928497).

USE OF NOACs AFTER WATCHMAN IMPLANTATION

As previously stated, in the PROTECT AF and PREVAIL randomized clinical trials, warfarin with a target international normalized ratio between 2 and 3 was typically given for 45 days after LAA occlusion with Watchman, thereby representing the most studied drug in this setting and the standard medical treatment for the prevention of DAT.

However, the use of warfarin is complicated by its narrow therapeutic window, the need for repeated blood testing and drug-drug and drug-food interactions. NOACs have proven to be safer than and as effective as warfarin for stroke prevention in AF patients in recent large randomized trials.¹⁵ Because NOACs are easier to use and initiate in clinical practice, they may represent an interesting alternative to warfarin after LAA occlusion with Watchman.

In a small, pilot, single-center registry, 18 patients received NOAC therapy during the first 45 days after Watchman implantation (dabigatran 110 mg twice daily in 16 patients and rivaroxaban 20 mg per day in two patients), and there were no cases of DAT at 45 days on TEE follow-up.¹⁶ In a second single-center study, 98 patients underwent concomitant AF ablation and LAA occlusion with Watchman. The postimplantation treatment strategy consisted of the use of warfarin in 37 patients, dabigatran in 34 patients, and rivaroxaban in 27 patients (61 patients on NOAC therapy). Incidental DAT was detected in two patients (both in the NOAC group) at 7 days and 6 weeks postimplantation. Both patients were asymptomatic, and the thrombus resolved by continuing the same anticoagulation regimen.¹⁷

In a recent large, retrospective, multicenter registry, 214 patients who underwent Watchman implantation received NOACs (46% apixaban, 46% rivaroxaban, 7% dabigatran, and 1% edoxaban) in either an uninterrupted (82%) or a single-held dose (16%) strategy. TEE or chest CT was performed between 6 weeks and 4 months postimplantation to assess for the presence of DAT. As compared to a control group of 212 patients with uninterrupted warfarin, the investigators found no significant difference in the rate of periprocedural complications (2.8% vs 2.4%; $P > .99$), DAT (1.4% vs 0.9%; $P > .99$), or postprocedural bleeding events (0.5% vs 0.9%; $P = .6$).¹⁸ In the EWOLUTION registry, 113 patients received NOACs after Watchman implantation (dabigatran, rivaroxaban, and apixaban) and a DAT rate of 1.4% at 3 months.¹⁹

Taken together, these results suggest that the use of NOACs may represent a safe and effective peri- and post-procedural alternative to warfarin for preventing DAT. These favorable preliminary results should be validated in a dedicated prospective randomized comparison of NOAC versus warfarin therapy after Watchman implantation.

CONCLUSION

The optimal antithrombotic regimen and its duration after Watchman implantation has yet to be determined. This treatment could be tailored according to the individual patient's risk of DAT and bleeding, and antiplatelet

agents could be used for patients with a high bleeding risk. In patients eligible for OAT, preliminary data have shown that NOACs may represent an interesting alternative to Warfarin after Watchman implantation. Larger clinical trials are needed to confirm the safety and efficacy of NOACs over warfarin in this setting. ■

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