Emerging Options for Anticoagulation in LAA Closure

Managing anticoagulation and antiplatelet therapy in patients undergoing percutaneous left atrial appendage closure with the Watchman device.

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Atrial fibrillation (AF) affects approximately 33 million people worldwide.[1] It is associated with a 1.5- to 2-fold increased risk of all-cause mortality and an increase in morbidity. Development of thrombi in the left atrial appendage (LAA) caused by blood stasis contributes to an elevated risk of ischemic stroke. Risk prediction tools, such as the CHA2DS2-VASc score, help clinicians determine which patients are at the highest risk for stroke. Generally, patients with a CHA2DS2-VASc score ≥ 2 are prescribed oral anticoagulation (OAC).

Bleeding is the most predominant risk associated with the use of anticoagulants, thus bleeding risk stratification tools and clinical judgment are used to assess this risk.[1] When initiating OAC, the benefit must outweigh the patient's risk of bleeding.

For patients who are at high risk for both bleeding and stroke, current clinical guideline recommendations include LAA occlusion and exclusion.[1] Surgical LAA occlusion or exclusion can be performed during concomitant cardiac surgery (ie, coronary artery bypass grafting, valve replacement). However, although this procedure has been used for decades, its use is limited due to the invasiveness of the procedure and because the literature is not clear on its benefit for stroke prevention. Interventional LAA occlusion and percutaneous LAA ligation have mainly been evaluated through observational studies and registries.

The Watchman device (Boston Scientific Corporation) was approved by the US Food and Drug Administration in 2015 to reduce the risk of thromboembolism from the LAA in patients with nonvalvular AF, making it a viable option for patients who are not suitable for long-term warfarin use.[2] To date, it is the only device to be compared in randomized trials with warfarin, the gold standard treatment option. Eligible patients still require short-term warfarin management—at least 45 days—and long-term antiplatelet therapy to prevent thrombosis. In this article, we aim to integrate the manufacturer's recommendations with published literature to develop a comprehensive approach to anticoagulant and antiplatelet therapy for patients undergoing percutaneous LAA closure.

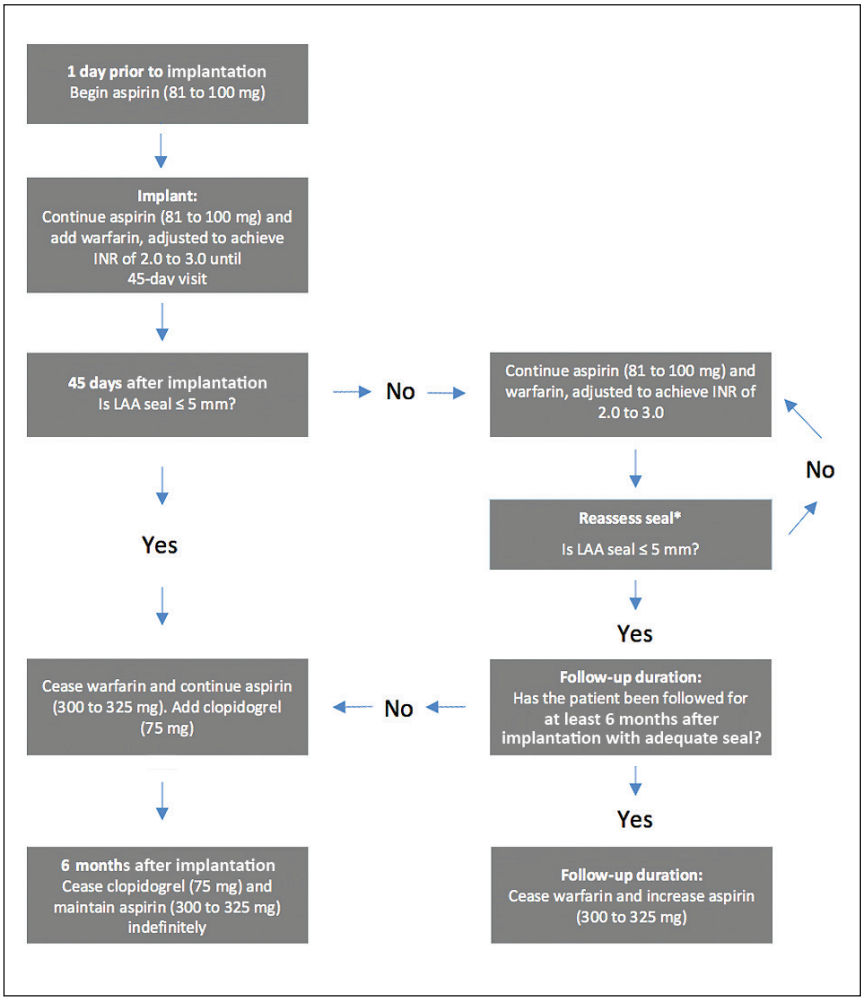
LANDMARK CLINICAL TRIALS

Currently, PROTECT AF and PREVAIL are the only two prospective, randomized controlled trials that have compared the Watchman device with traditional management using OAC for reducing the stroke risk in patients with AF.[3,4] Results of the PROTECT AF trial found Watchman to be noninferior to warfarin for the composite outcome of stroke, systemic embolism, and cardiovascular or unexplained death.[3] Watchman accounted for a significantly larger amount of safety events, which were a composite of major bleeding and procedure-related events. In the PREVAIL trial, investigators enrolled higher-risk patients and included periprocedural safety data.[4] This device did not meet the noninferiority criteria for the composite efficacy outcome of stroke, systemic embolism, and cardiovascular or unexplained death when including perioperative events. However, late ischemic composite efficacy (excluding the first 7 days following the procedure) met noninferiority and the early safety endpoints, as well as prespecified acceptable limits, which led to the device's approval in the United States.

Figure 1 shows the general pharmacotherapy recommendations from the manufacturer labeling, PROTECT AF, and PREVAIL.[2-4] Current manufacturer recommendations indicate that aspirin 81 to 100 mg daily should begin 1 day prior to the procedure and then continued indefinitely, mirroring PROTECT AF and PREVAIL.[1-5] During the procedure, the Watchman-approved labeling recommends patients receive

heparin to achieve a minimum activated clotting time (ACT) of 200 to 300 seconds.[2] During the PROTECT AF trial, heparin was administered as a bolus to achieve an ACT > 250 seconds, and if the procedure time exceeded 60 minutes, an additional bolus of heparin was given to maintain an ACT > 250 seconds.[6] The study utilized a bolus rather than continuous infusion due to the short duration of the procedure.

During both trials, warfarin was given to patients postprocedurally for at least 45 days to prevent thrombosis while endothelialization occured.[2-4] The device labeling complements this practice by recommending anticoagulation for 45 days after the procedure if there is closure of the LAA.[2] There are no recommendations made for initiating warfarin before the procedure. Patients in PROTECT and PREVAIL were already receiving anticoagulation prior to enrollment.[3,4] The PROTECT AF study protocol specified that a patient's international normalized ratio (INR) should be < 2 before the procedure, thus not allowing a therapeutic INR but acknowledging initiation before device implantation.[3-5,7]



Courtesy of Boston Scientific Corporation.

Figure 1. Pharmacologic regimen for Watchman device implantation. *The performance and timing of TEE to reevaluate the LAA seal is left to physician discretion. INR, international normalized ratio; LAA, left atrial appendage. Image provided courtesy of © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.

After postprocedural day 45, transesophageal echocardiography (TEE) is recommended to identify any device-related thrombus (DRT) and to assess for closure of the device within the LAA, defined as peridevice flow < 5 mm.[2-4]

If a seal has formed and no DRT is found, warfarin can be discontinued, and the patient should initiate use of clopidogrel 75 mg daily until 6 months postprocedure. When discontinuing warfarin, the package insert, along with PROTECT AF and PREVAIL, all recommend increasing the dosage of aspirin to 325 mg daily; however, this was not mandatory in the trial protocols.

If a seal does not form or DRT occurs, it is recommended that warfarin be continued until the issue is resolved. It is at the physician's discretion as to when TEE should be performed to reevaluate the device's seal and for DRT.[2-4] Once a seal is formed or the DRT has resolved, warfarin can be discontinued, aspirin increased, and clopidogrel initiated. Clopidogrel should be continued up to 6 months postprocedure. Monotherapy with aspirin should be used ≥ 6 months postprocedure once warfarin has been discontinued.

ALTERNATE ANTICOAGULATION REGIMENS

Novel Oral Anticoagulants

Warfarin was the only OAC used in the randomized controlled trials for the Watchman device, because the first novel oral anticoagulant (NOAC), dabigatran, had not yet been approved for use in AF until after PROTECT AF was published.[3,8] Device labeling has a precautionary warning about the use of anticoagulants other than warfarin, in part due to the RE-ALIGN trial, which found that patients with mechanical heart valves had an increased thromboembolic risk and bleeding complications, in addition to the lack of randomized controlled data.[2,9] Given the complexity of warfarin manage-

ment and the decreased need for laboratory monitoring of NOACs, several studies have investigated the use of NOACs for thromboprophylaxis following Watchman device implantation.[10-12]

A recently published retrospective, multicenter study by Enomoto et al evaluated the feasibility and safety of using NOACs compared with warfarin.[10] Of the 214 patients who received a NOAC, 82% started a NOAC prior to surgery without holding a dose, 16% held one dose prior to the procedure, and 2% initiated use after the procedure. The NOAC group was compared with 212 patients who received warfarin, as stated in Table 1. Periprocedural thromboembolic and bleeding complications were not significantly different between groups. Following implantation, the endpoints of DRT, or a composite of thromboembolism and DRT, and bleeding events were similar between groups. The average CHA2DS2-VASc score was 3.8 and 4.2 in the NOAC and warfarin groups, respectively. The average HAS-BLED score was 2.4 and 2.7 in the NOAC and warfarin groups, respectively. See Table 1 for details regarding antiplatelet therapy.

Warfarin may not be an option for all patients due to the logistics of managing a patient's INR or contraindications other than bleeding. Despite the lack of randomized trials and the implications RE-ALIGN may have, a NOAC could be an

TABLE 1. ANTICOAGULATION DATA SUMMARY

Study	Preimplantation	Implantation Day	Initial 45 Days After Implantation
Watchman labeling[2]	1 day before, start ASA 81–100 mg daily	Add warfarin	ASA 81 mg daily; warfarin INR 2–3
PROTECT AF[3]	If taking warfarin INR < 2: 1 day before, start ASA 81–100 mg daily	Not specified	ASA 81 mg daily; warfarin INR 2–3
PREVAIL[4]			
Bosche et al[12]	Not specified	Not specified	OAC contraindicated or on DAPT: ASA 100 mg, clopidogrel 75 mg; no indications to OAC: dabigatran 110 mg twice daily or rivaroxaban 20 mg daily
Enomoto et al[10]	Variable	Variable, typically on full OAC	All: ASA; control: warfarin INR 2–3; NOAC: dabigatran, rivaroxaban, apixaban, or edoxaban
Barakat et al[11]	ASA 81 mg daily; warfarin 4–5 days prior; NOAC 24–48 hours prior	Warfarin: continue OAC; NOAC: hold 1 dose immediately prior to surgery	All: ASA and OAC; warfarin (INR 2–3); or apixaban 5 mg twice daily (n = 1) or dabigatran 150 mg twice daily (n = 1)
ASAP[13]	None	None	ASA and clopidogrel 75 mg or ticiopidine
Meincke et al[14]	Not specified	Not specified	OAC contraindication: ASA 100 mg daily and clopidogrel 75 mg; control: ASA 100 mg daily and warfarin INR 2–3

Abbreviations: AF, atrial fibrillation; ASA, aspirin; CVA, cerebral vascular accident; DAPT, dual antiplatelet therapy; DRT, drug-related thrombosis; GI, gastrointestinal; INR, international normalized ratio; N/A, not applicable; NOAC, novel oral anticoagulant; OAC, oral anticoagulant; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

alternative option. Because of the higher quality of data available on its use as thromboprophylaxis, our institution initiates or continues warfarin therapy. However, should a patient already be prescribed NOAC therapy, it is our policy to continue the NOAC rather than switch to warfarin in order to maintain continuity of treatment.[10-12]

Dual Antiplatelet Therapy

PROTECT AF and PREVAIL did not enroll patients who were unable to receive warfarin therapy, and current labeling recommends that only patients suitable for anticoagulation with warfarin may receive the Watchman device.[2-4] The device is appropriate for patients who have relative contraindications to long-term OACs. Literature assessing the use of Watchman in patients receiving only dual antiplatelet therapy (DAPT) could make the device available to another population of patients who have an absolute contraindication to OACs.[2,13]

The ASAP study evaluated the use of aspirin with clopidogrel or ticiopidine for 6 months postprocedure followed by monotherapy with aspirin indefinitely.[13] The study was a multicenter, prospective, nonrandomized trial that enrolled 150 patients to receive DAPT only. All-cause stroke or systemic embolism occurred in four patients (2.3% per year). The

	45 Days to 6 Months After Implantation		Long-Term (> 6 Months) Follow-Up	Outcomes
	Seal and No DRT	No Seal or DRT		
	Discontinue warfarin ASA 300–325 mg daily; add clopidogrel 75 mg daily	Continue ASA 81 plus warfarin; reassess with TEE (timing is physician's choice); if < 6 months at time of reassessment, discontinue warfarin, increase aspirin to 300–325 mg daily, and start clopidogrel 75 mg daily until at least 6 months postimplantation	ASA 300–325 mg daily	N/A
	Discontinue warfarin, increase ASA 300–325 mg daily, and add clopidogrel 75 mg daily	Continue ASA 81 mg plus warfarin; reassess seal (timing is physician's choice or 6 months); if < 6 months at time of reassessment, discontinue warfarin, increase aspirin to 300–325 mg daily, and start clopidogrel 75 mg daily until at least 6 months postimplantation	ASA 81–325 mg daily	Noninferior to warfarin
				Noninferior to warfarin if excluding first 7 days after procedure
	All: ASA 100 mg daily plus clopidogrel 75 mg daily	DAPT: ASA 100 mg daily and clopidogrel 75 mg daily; OAC: dabigatran or rivaroxaban plus ASA 100 mg daily continued; reassessment period not specified	ASA 100 mg daily	27 on DAPT, 18 on NOACs; 0 TIA/CVA 0 thrombus, 6 major bleeds (3 in each group)
	All: ASA daily and clopidogrel 75 mg daily	Continue ASA and OAC or restart if stopped; first follow-up TEE assessing seal and DRT at 7 days and 45 days–6 months postimplantation; no mention of TEE reassessment	ASA daily	Periprocedural and follow-up thromboembolism; bleeding not significantly different between groups
	All: ASA daily and clopidogrel 75 mg daily	Planned ASA daily and OAC for full 6 months; no mention of TEE reassessment; no mention of DRT	ASA daily	No major bleeding; 3 minor GI bleeds
	ASA and clopidogrel or ticiopidine; seal assessment not reported	No specification for seal	ASA	Stroke or systemic embolism, 2.3% per year; hemorrhagic stroke, 0.6% per year
	DAPT high bleeding risk: ASA and clopidogrel for 3 months, then ASA daily; DAPT low to moderate bleeding risk: ASA and clopidogrel for 6 months; OAC: DAPT for 4 months	TEE at 3 and 6 months; DAPT: 3 additional months of ASA and clopidogrel; OAC: additional 45 days of warfarin	ASA	Perioprocedural: 3.3% pericardial effusion, 1.7% ischemic stroke; long-term: 1.7% TIA; no major bleeds

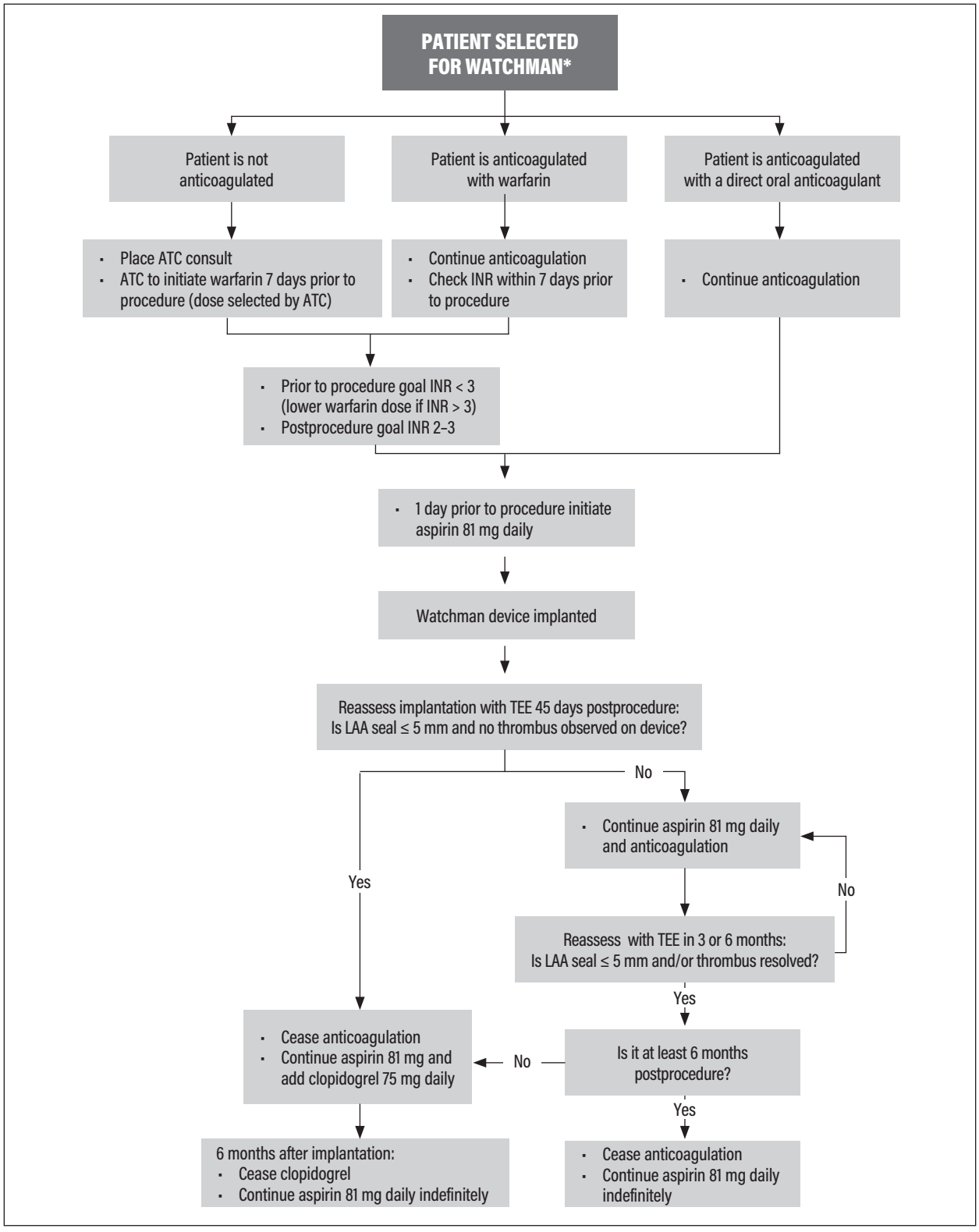


Figure 2. University of Illinois Hospital and Health Sciences System's Watchman pharmacologic regimen. *Note: Patients with other long-term indications for anticoagulation or contraindications to short-term anticoagulation are not candidates for the Watchman device. Abbreviations: ATC, antithrombosis clinic; INR, international normalized ratio; LAA, left atrial appendage; TEE, transesophageal echocardiography.

mean CHADS2 score was 2.8, which estimated a 7.5% stroke risk annually. An observed ischemic stroke rate of 1.7% per year is 77% lower than expected.

Patients can only receive the Watchman device if they are good candidates for short-term OAC, which in turn excludes a patient population whom could greatly benefit. For this group of patients, the benefit of the device may significantly outweigh the risk of no anticoagulation. However, because of the paucity of data with DAPT therapy, patients must be on an OAC at our institution.

INSTITUTIONAL PROTOCOL

Figure 2 depicts the algorithm in use at our institution for treating patients with the Watchman device. In a real-world setting, patients are likely not taking warfarin because they have been deemed unsuitable candidates. Because it can take a considerable amount of time relative to the 45 days of therapy to achieve a goal INR of 2 to 3, it is our opinion that starting warfarin at least 7 days prior to device implantation is the safest practice to expedite a therapeutic INR and reduce the risk of device thrombi. Furthermore, our institution's algorithm (Figure 2) allows for an INR of up to 3 during implantation. This mimics guidelines for catheter ablation.[1]

Follow-up with TEE and the timing of transitioning anticoagulation to DAPT is very similar to the Watchman labeling, PROTECT AF, and PREVAIL.[3,4] However, the benefits of increasing aspirin to 325 mg once OAC is discontinued are unclear. For this reason, we maintain the aspirin dose at 81 mg; both PROTECT AF and PREVAIL did not require aspirin to be increased to 325 mg when transitioning to DAPT. All of the literature considered for the creation of our algorithm can be found in Table 1.

CONCLUSION

Although the Watchman device is a potential option for patients who cannot tolerate long-term anticoagulation, the current manufacturer guidelines require an intensive regimen including warfarin, DAPT, and high-dose aspirin. Since the completion of the landmark trials, investigators have explored off-label anticoagulation regimens with NOACs and DAPT. We have attempted to coalesce the current evidence into a single, comprehensive, and practical review that clinicians can refer to in their management of this growing patient population. ■

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