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Review Article

The WATCHMAN device and post-implantation anticoagulation management. A review of key studies and the risk of device-related thrombosis

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Abstract: Background: Ischemic stroke is a devastating complication of atrial fibrillation (Afib). Anticoagulation is the gold standard to prevent stroke and systemic embolization. However, many patients have a contraindication to oral anticoagulation. The WATCHMAN device, which closes the left atrial appendage, is non-inferior to warfarin to prevent embolic events in clinical trials. Post-procedural anticoagulation is needed to avoid device-related thrombosis. The use of anticoagulants after WATCHMAN implantation in patients with high bleeding risks has been a source of debate. Objective: This article summarizes the current evidence on anticoagulation following the implantation of the WATCHMAN device, focusing on patients who have an absolute contraindication to oral anticoagulation. Observation: The WATCHMAN device is efficacious and safe in preventing stroke and systemic embolization. Warfarin and aspirin are given for 45 days after implantation. If TEE at 45 days shows minimal residual peri-device flow (≤ 5mm) and no device-related thrombus, warfarin is stopped. This is followed by aspirin and clopidogrel for six months, then aspirin indefinitely. Antithrombotic therapy with aspirin and clopidogrel for six months followed by daily aspirin indefinitely may be feasible for patients with an absolute contraindication to OAC. DOACs are more convenient to use than warfarin, and limited evidence suggests that they are not inferior following implantation of the device. Conclusion: Following the WATCHMAN implantation, the most often utilized regimen is warfarin followed by antiplatelet treatment. In cases where there is a high risk of bleeding, antiplatelets alone may be sufficient. More research is needed to tailor the existing antithrombotic regimen to the needs of patients.

Keywords: Atrial fibrillation, LAA closure, WATCHMAN device, anticoagulation, device related thrombosis

Introduction

The global burden of (A.fib) has increased significantly because of an aging global population. Life expectancy has increased for both men and women, rising from 58 years in 1970 to 73 years in 2020. This explains why the prevalence of A.fib tripled in the last 50 years [1]. By 2030, the United States may have over 12 million people with atrial fibrillation [2]. A.fib is linked to 3-fold increased risk of heart failure, a 5-fold increased risk of stroke, a 2-fold increased risk of dementia, and a 1.5-1.9-fold increased chance of death. As a result, treatment and prevention of consequences are critical [3]. Direct oral anticoagulants (DOACs) are the current gold standard for thromboembolism prevention, except for patients with moderate to severe mitral stenosis or a mechanical heart valve, for whom warfarin is the sole medicine advised. The increasing number of patients with a higher risk for bleeding was associated with increased use of left atrial appendage (LAA) occlusion as a non-pharmacological therapy for stroke prevention. The WATCHMAN device was licensed by the US Food and Drug Administration (FDA) in 2015 as the first percutaneous LAA closure device alternative to long-term anticoagulation in non-valvular atrial fibrillation (NVAF) to prevent left

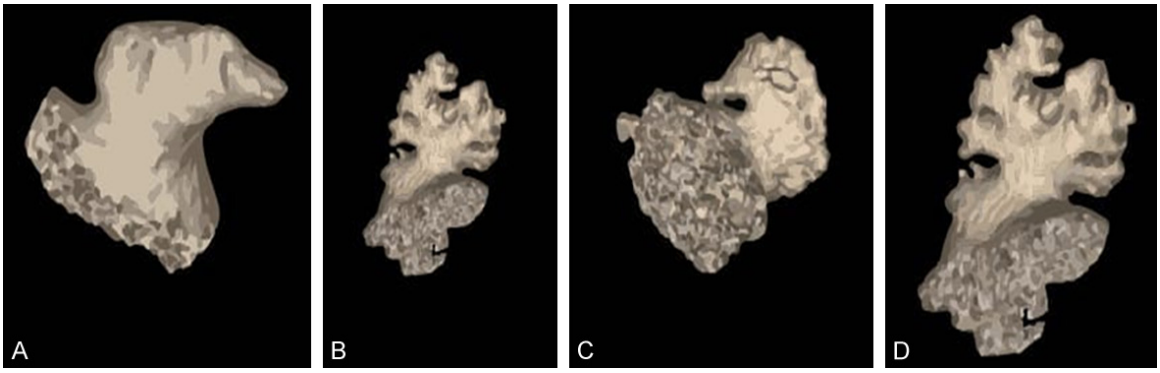

Figure 1. *The* different morphologies of the LAA. A: Windsock; B: Cactus; C: Chicken wing; D: Cauliflower.

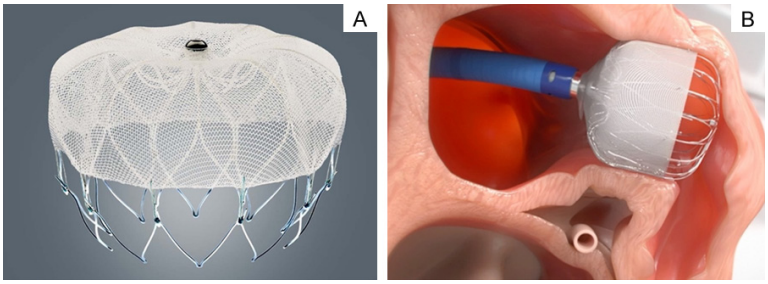

Figure 2. A: *The* parachute shaped WATCHMAN device. B: The device seals the left atrial appendage.

atrial thromboembolism. On the other hand, short-term anticoagulation after implantation is challenging in a patient with a high risk of bleeding. This page outlines the most important research on the WATCHMAN device, including efficacy, anticoagulation strategy, bleeding problems, and device-related thrombosis.

Morphology of LAA and pathophysiology of thrombus formation

The LAA is a trabecular finger-like projection arising from the body of the left atrium, mostly between the anterior and lateral walls. It comprises an orifice, neck, and body. Protrusions are coming out of the body, defined as lobes. In one study, one lobe was found in 24 patients (68%), two lobes in 12 patients (24%), three lobes in 3 patients (6%), and four lobes in 1 patient (2%) [4]. There are 4 identified LAA morphologies: "Chicken Wing", "Cactus", "Windsock", and "Cauliflower" (**Figure 1**). Chicken wing is the most common morphology (48%), and it has a dominant lobe that bends in the middle. They found it to have the lowest risk for thrombus formation.

On the other hand, cauliflower, the least common (3%), carries the highest risk of thrombosis because of the variable number of lobes, the short length, and more complex internal characteristics [5].

When the atrium fibrillates, there is a decrease in contractility, which generates a state of stagnation and predisposes to thrombus formation. In over 90% of patients with A.fib, LAA is the most common site of thrombus formation. In addition, LAA morphology has a significant association with the risk of stroke in AF patients. Larger LAA volume, number of lobes, more extended LAA depth, orifice size and extensive LAA trabeculation are associated with a higher risk of stroke/TIA [6, 7].

The WATCHMAN is a parachute-shaped device inserted over a sheath through a peripheral vein. Then it self expands to close off the left atrial appendage where the blood clot tends to form (**Figure 2**).

Key trials and studies for the WATCHMAN device and the anticoagulation regimen

PROTECT-AF and PREVAIL trials

The PROTECT-AF trial [8] is the pivotal non-inferiority RCT to assess the efficacy and safety of WATCHMAN device compared to OAC in NVAF. The device was non-inferior to long-term warfarin treatment in reducing cardiovascular death, stroke, and systemic embolism in NVAF. However, periprocedural safety hazards, such

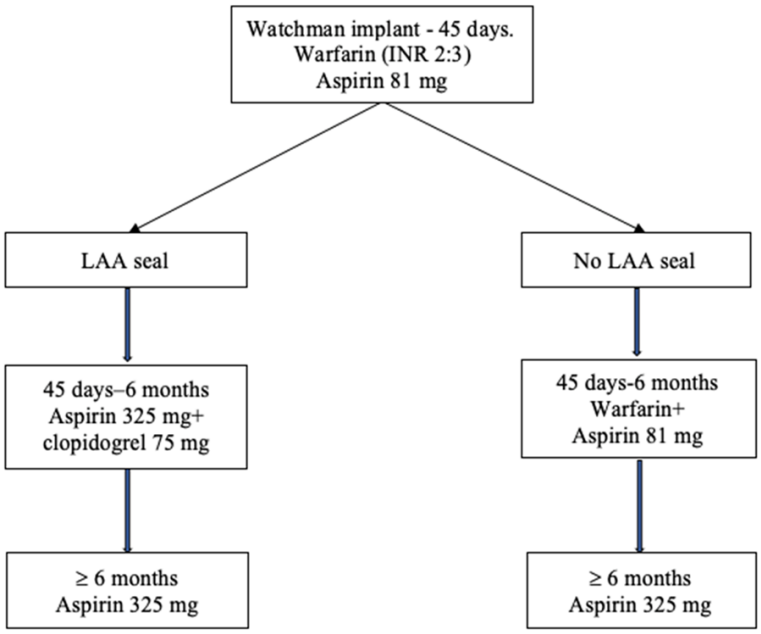

Figure 3. A simplified diagram of the anticoagulation protocol in the PROTECT-AF and PREVAIL trials.

as pericardial effusion, procedure-related stroke, air embolism, and device embolization, were associated with the device implantation.

The PREVAIL trial [9], a prospective randomized non-inferiority intention-to-treat trial, aimed to address the limitations of the PROTECT AF study and provide reassurance of the safety and effectiveness of the WATCHMAN device after the reported periprocedural air embolism. The majority of the serious side effects in the PROTECT-AF trial occurred during the periprocedural period. Therefore, The PREVAIL trial included a co-primary end event and a hypothesis testing to evaluate for major adverse events from randomization to within seven days of the device implantation.

The PREVAIL study found that the WATCHMAN device is non-inferior to warfarin in lowering composite of ischemic stroke or embolization more than seven days after randomization, composite all-cause mortality, ischemic stroke, systemic embolization, or device-related events required major interventions within seven days of the procedure.

Procedure-related complications decreased in this trial compared to the PROTECT-AF from 8.7% to 4.2% in the first 7 days after the implantation (P=0.004). Those include pericardial effusions requiring surgical repair {1.6% to 0.4% (P=0.027)} and procedural and device-related strokes {1.1% to 0.4% (P=0.007)}.

The anticoagulation protocol (**Figure 3**) in both studies was warfarin and 81 mg aspirin for 45 days after implantation. If the 45-day TEE showed LAA seal, which defined as either complete closure of the LAA, or if residual peri device flow was <5 mm in width and there was no definite visible large thrombus on the device, warfarin was discontinued followed by dual antiplatelet therapy (DAPT) with aspirin (81-325 mg) and clopidogrel 75 mg for six months, followed by single antiplatelet therapy (SAPT) with aspirin 325 mg indefinitely.

An extended follow-up on the PROTECT-AF trial for up to 5 years supported the non-inferiority of LAA closure over the standard warfarin to prevent ischemic stroke and systemic embolization and superiority for cardiovascular and all-cause mortality [10].

CAP and CAP2 [11]

Continued access to PROTECT-AF (CAP) and constant access to PREVAIL (CAP2) are two registries to evaluate the efficacy and safety of the WATCHMAN device after a prolonged follow-up (4.5-5 years). Compared to the expected risk of ischemic stroke based on the CHADS2VASC score, CAP and CAP2 demonstrated a 78% and 69% ischemic stroke relative risk reduction, respectively, after LAA closure.

In the CAP, device-related thrombus was reported in 14 patients (2.6%); 2 of them had ischemic stroke symptoms. In the CAP2, 21 patients had DRT (3.9%), and four patients experienced ischemic stroke. Thus, the device thrombus-related stroke rate was 0.1 in CAP and 0.2 in CAP2 per 100 patient-years.

The ASAP trial

Although the PROTECT-AF and PREVAIL trials demonstrated excellent efficacy of LAA closure by WATCHMAN device for stroke and embolization prevention, both included patients eligible for six weeks of warfarin after the implantation.

The ASAP [12] addressed the population with a high risk of bleeding and absolute contraindication to warfarin. The most common contraindications in the study were, 1: A bleeding tendency that includes active peptic ulcer disease, history of gastrointestinal hemorrhage, respiratory tract hemorrhage, genitourinary hemorrhage, central nervous system hemorrhage, history of cerebral aneurysm, aortic dissection or pericarditis, and pericardial effusion. 2: Blood dyscrasias. 3: Patients with a high risk of falls.

It is a non-randomized trial that included 150 patients with NVAF and CHADS2 ≥1 who are ineligible for short-term warfarin therapy. The patient received Plavix or ticlopidine for six months and aspirin for lifelong. The results showed that all-cause stroke or systemic embolism was 2.3% per year, ischemic stroke 1.7% per year, hemorrhagic stroke 0.6% per year. The average CHADS2 score in the study was 2.8, and the expected risk of ischemic stroke was 7.4%. However, surprisingly, the ischemic stroke rate in the study was 1.7%, which equals 77% fewer events than expected.

The rate of ischemic stroke was nearly equal to the PROTECT-AF trial; Suggesting that LAA closure with the WATCHMAN device can be performed without warfarin transition and can be a good alternative while considering preventive therapies for stroke in NVAF patients with contraindications to systemic oral anticoagulation. In this trial, the DRT occurred in 6 patients (4%), and only one patient had an ischemic stroke (0.7%).

EWOLUTION trial [13, 14]

In the EWOLUTION (WATCHMAN Outcomes in Real-Life Utilization) registry, 1020 patients from multiple centers in Europe were followed after the watchman procedure. The study enrolled patients with CHA2DS2VASc (mean, 4.5±1.6) and HAS-BLED (mean, 2.3±1.2) scores. Compared to the PROTECT-AF and the PREVAIL trials, the population here has a higher risk of thromboembolism and bleeding.

Anticoagulation following LAA occlusion was variable in these patients. It included warfarin in 16% of patients, direct oral anticoagulants (DOACs) in 11%, dual antiplatelet therapy in 60%, single antiplatelet therapy in 7%, and no anticoagulation in 6% of patients. Notably, 72% of the patient was ineligible to OAC and switched directly after the procedure to DAPT or nothing. At 6 and 48 months, 66% and 84% were on SAPT or nothing, respectively.

Studying the data, Neither DAPT nor DOAC therapy showed any inferiority to warfarin in terms of outcome, including stroke or bleeding. Compared to the other RCTs, DRT in the total population of the EWOLUTION trial was 4.1%, almost similar to the 3.7% observed in other studies where warfarin was used, even though the average CHADVASC2 and HAS-BLED score was higher in EWOLUTION compared to other RCTs. In the trial, there was no statistically significant relation between DRT and type of anticoagulation. Moreover, there was no significant difference in the annual rate of ischemic stroke or systemic embolization related to the presence of DRT.

Of interest, the major non-procedural bleeding in the trial was 2.7%, with a 46% relative risk reduction compared to warfarin. Patients who discontinued the DAPT less than 105 days had the lowest risk of bleeding, 1.1%, compared to 3.5% if the DAPT continued more than 105 days. Interestingly, the risk of ischemic stroke, systemic embolization, and DRT was statistically non-significant between both groups, solidifying the use of DAPT for a shorter duration in patients with a very high risk of bleeding.

DOACs after watchman implantation

DOACs have shown superiority over warfarin for stroke prevention in NVAF. In both the PROTECT-AF and PREVAIL trials, warfarin was the anticoagulant of choice. However, warfarin use has several limitations, including regular blood tests, drug-drug interaction, and interpersonal drug response variability. Hence, there have been multiple retrospectives and obser-

vational studies looking at DOACS for post-device anticoagulation.

A small single-center registry enrolled 45 patients after successful WATCHMAN device implantation [15]. Eighteen patients received DOACs (rivaroxaban 20 mg or dabigatran 110 mg twice daily) for at least 45 days, then aspirin 100 mg and clopidogrel 75 mg for 6 months followed by aspirin 100 mg only. The other 27 patients received DAPT for 6 months, followed by aspirin 100 mg. The study concluded the DOACs are safe and effective in the first 45 days after the device implantation. However, the population number was small, and there was no comparison against the warfarin. Of note, device-related thrombosis was not reported in any patient during the follow-up.

A multicenter retrospective analysis by Enomoto Y. [16] gave 214 patients DOACs after the procedure. Around 46% of patients received apixaban, 46% received rivaroxaban, 7% dabigatran, and 1% edoxaban. The control group had 212 patients who received warfarin. They were followed up with CT or TEE in 6 weeks and four months for device-associated thrombus. The rate of DRT or thromboembolic events was comparable between both groups (0.9% vs. 0.5%, P=1). Furthermore, there was no statistically significant difference in the postprocedure bleeding between both groups.

It was concluded that peri- and post-procedural DOAC administration was a safe substitute for warfarin without an absolute increase in the risk of bleeding. There must be larger randomized controlled trials to validate the findings, but the preliminary results suggest that DOACS is an excellent choice and non-inferior to warfarin [17-19].

Device related thrombosis (DRT)

Device-related thrombosis is one of the concerning complications following the watchman device implantation. Therefore, anticoagulation is recommended for six weeks. In the PROTECT-AF trial, the incidence of DRT was initially 4.2%. A study by Michael L. Main [20] evaluated 93 TEE in 35 PROTECT-AF device patients in three phases of ECHO assessment, and the actual incidence of DRT was 5.7, and it was less likely during the first 45 days.

Another study by Dukkipati, Srinivas [21] evaluated the incidence and characteristics of DRT following WATCHMAN device implantation in patients enrolled in PROTECT-AF, PREVAIL, CAP, or CAP2 trials. The incidence of DRT was 3.74%. Ischemic stroke and systemic embolization rate associated with DRT was 25% compared to 6.8% in patients without DRT, which means the risk increases over three folds in patients with DRT. The all-cause or cardiovascular mortality was similar between both groups. Patients with a history of permeant AF, TIA/Stroke, vascular disease, larger atrial diameter, or lower ejection fraction were at higher risk of DRT.

Kubo, Shunsuke et al. [22] followed up 119 patients with atrial fibrillation after watchman device implantation and assessed the incidence of DRT. The incidence in the study was 3.4%. Factors related to higher DRT were chronic atrial fibrillation, device size, off-protocol anticoagulation regimen. The standard anticoagulation was as illustrated in the PROTECT-AF trial. All the patients who had the device thrombosis have deviated from the anticoagulation protocol. After detecting the thrombus by the TEE, warfarin and aspirin continued or restarted, and follow-up TEE was scheduled at fixed intervals to see the thrombus resolution. All thrombi resolved in the next TEE, and warfarin was discontinued within six months of detecting thrombi. There was no incidence of systemic embolization or deaths in all the patients. **Table 1** is showing the incidence of DRT in the trials mentioned above and the anticoagulation regimen in each study.

Bleeding outcomes

Although oral anticoagulation is excellent at reducing the risk of thromboembolism, bleeding is a worrisome complication. A pooled analysis of PROTECT-AF and PREVAIL trials by Price, Matthew [23] showed no difference in primary bleeding rate between LAAC and long-term warfarin at a three-year follow-up. However, LAAC was associated with a significant decrease in the rate of substantial bleeding once the adjunct anticoagulation and the complete DAPT duration. After the first six months, when aspirin only continued, LAAC is associated with 72% relative risk reduction in major bleeding, mainly gastrointestinal bleed-

Table 1. The incidence of device-related thrombosis and the anticoagulation protocol in the key trials of the WATCHMAN device

Trial/study	Population	Follow up	Anticoagulation	DRT
PROTECT-AF [8]	707	18 months	Warfarin and aspirin (81 mg) for 45 days, then aspirin (81-325 mg) & Clopidogrel for 6 months followed by aspirin	4.2%
PREVAIL trial [9]	407	18 months		Not reported
CAP [11]	566	50 months		2.6%
CAP2 [11]	578	50 months		3.9%
Dukkipati, Srinivas R et al. [21]	1739	na		3.7%
Kubo, Shunsuke et al. [22]	119	1,456±546 days		3.4%
EWOLUTION [13, 14]	1020	24 months	warfarin (16%) DOACs (11%) DAPT (60%) SAPT (7%) no anticoagulation (6%)	4.1%
ASAP [12]	150	14.4±8.6 months	Clopidogrel for 6 months and aspirin for life	4%
Enomoto Y [16]	426		NOAC vs. Warfarin	0.9% vs. 0.5%, P=1
Bösche, Leif I et al. [15]	45	417±323 days	NOAC vs. DAPT	0%

ing and to a lesser degree intracranial bleeding.

Current guidelines recommendations

AHA/ACC 2019 focused update on 2014 guidelines and ESC 2020 [24, 25] recommended: WATCHMAN device for patients with NVAF who have an increased risk of thromboembolism (CHA_2DS_2VASc score ≥3) and contraindication for long-term anticoagulation (Class IIb). Surgical LAA occlusion may be considered in patients with A.fib undergoing cardiac surgery (Class IIb).

Future studies

ASAP-TOO

ASAP-TOO [26] (Assessment of the WATCHMAN device in patients unsuitable for oral anticoagulation) randomized patients to a device or control group. Patients in the device group take aspirin the day before the procedure, then continued daily. In the control group, patients either receive aspirin or no therapy. The study aims to evaluate the efficacy and safety of WATCHMAN devices in the ineligible population to oral anticoagulation and compare the device to single or no antiplatelet therapy.

The CHAMPION-AF trial

The CHAMPION-AF [27] is a unique trial that evaluates the LAAC with WATCHMAN device for the first time versus DOACs as the first line to reduce the risk of ischemic stroke in patients with NVAF. The study aim is that even patients who have tolerated anticoagulation are still at risk of bleeding. WATCHMAN device would provide them with stroke risk reduction without bleeding risk.

AMULET IDE trial [28]

This study was designed to evaluate the efficacy and safety of the AMPLATZER™ Amulet™ device compared to The WATCHMAN. The Amulet occluder has the advantage of a dual seal mechanism which provides complete and immediate LAA occlusion. The study showed that the Amulet occluder is non-inferior to the WATCHMAN for safety and efficacy. The antithrombotic regimen at the time of discharge was either DAPT or aspirin plus OAC. In the Amulet arm, 21% of patients were discharged on OAC, and around 96% of the WATCHMAN's arm received anticoagulation. This may Favor the Amulet for NVAF with contraindication to anticoagulation. The FDA in 2021 has approved the Amulet occluder for stroke prevention in patients with NVAF [29].

Conclusion

The best anticoagulant management following implantation of the WATCHMAN device is still unknown. In the first 45 days, warfarin and aspirin are the most often utilized medications, followed by six months of DAPT from the day of the procedure and then lifelong aspirin. Among individuals with absolute contraindications to

oral anticoagulants, DAPT is safe and effective for six months after device implantation, followed by aspirin. DOACs are thought to be more user-friendly than warfarin, and several observational studies have shown that they are non-inferior in terms of embolic events and bleeding risk; nevertheless, bigger RCTs are needed to confirm the findings. The WATCHMAN device reduces the risk of bleeding, especially after quitting warfarin and using dual antiplatelet therapy for a shorter period. Single antiplatelet medication after implantation is now being researched to accommodate more patients with a high risk of bleeding.

Disclosure of conflict of interest

None.

Abbreviations

LAA, Left atrial appendage; LAAC, Left atrial appendage closure; NVAF, Non valvular atrial fibrillation; OAC, Oral anticoagulant (this includes warfarin and direct oral anticoagulants); Afib, atrial fibrillation; DOAC, Direct oral anticoagulant; SAPT, Single antiplatelet therapy; DAPT, Dual antiplatelet therapy; DRT, Device related thrombosis; RCT, randomized controlled trial.

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