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REVIEW ARTICLE

The WATCHMAN Device Review: A New Era for Stroke Prophylaxis

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Abstract

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, accounting for more than 37 million cases worldwide. In AF, the left atrial appendage (LAA) is the most common site of thrombus formation, and its ligation/closure with the WATCHMAN device is a good alternative to long-term oral anticoagulation, especially in patients with contraindications to warfarin. However, the implantation procedure is associated with various risks and complications. A short-term anticoagulant and antithrombotic administration are essential after implantation. However, no consensus has been reached on the optimal regimen. The WATCHMAN device is non-inferior to warfarin and is a safe alternative for the prevention of stroke and systemic embolization related to non-valvular atrial fibrillation (NVAF). Important procedure-related complications include pericardial effusion (PE), device embolization, procedure-related ischemic stroke, and device-related thrombosis (DRT) formation. It is essential to optimize post-implantation therapy according to individual patient bleeding risk, DRT formation, and contraindication to direct oral anticoagulants (DOACs). Recent studies have also shown that DOACs are a convenient and non-inferior substitute for warfarin. Furthermore, patients with absolute contraindications to OACs/DOACs can only be managed with dual antiplatelet therapy (DAPT). Transesophageal echocardiography (TEE) should be used to assess residual peridevice flow and possible DRT formation at days 45 and 12 months. Low molecular weight heparin (LMWH) and OAC are excellent choices for DRT treatment if detected. This review summarizes the most important complications of the WATCHMAN device in the existing literature and discusses various anticoagulation strategies and challenges post-implementation.

Keywords: Warfarin, DOAC, CVA, Thrombosis, AF

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accounting for more than 37 million cases of AF worldwide.[1] It is a major risk factor for ischemic stroke and causes significant economic burden, morbidity and mortality.[2] In patients with non-rheumatic AF, the left atrial appendage (LAA) is the site of more than 90% of all left atrial thrombi.[3,4] Although long-term oral anticoagulation with warfarin is recommended for most patients with AF, it may cause serious adverse effects, of which increased bleeding risk is the most notable.[5] Several recent trials have demonstrated the superiority of the new oral anticoagulants dabigatran, Rivaroxaban, and apixaban over standard warfarin therapy.[6–8] Nonetheless, even with these new agents, bleeding complications were significant and, in some ways, comparable to those

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seen with warfarin, with the exception of intracranial bleeding, which was less severe. A small number of patients discontinued drug therapy prematurely because of adverse events, most of which were gastrointestinal in nature, as in dabigatran patients. This has resulted in the development of a novel stroke prevention procedure as an alternative to anticoagulation therapy for patients with AF.

Because the LAA is a major source of thromboembolism in patients with AF, it was justified to ligate, amputate, or occlude the LAA, particularly in patients who had an indication for anticoagulation but were unable to take long-term oral anticoagulation. Three different devices specifically designed for occlusion of the LAA have been clinically evaluated: the percutaneous LAA transcatheter occlusion system (PLAATO), WATCHMAN system (Boston Scientific Corp., Natick, MA, United States), and AMPLATZER Cardiac Plug (St. Jude Medical, Inc., St. Paul, MN, United States). Although the safety and feasibility of the PLAATO device have been demonstrated in several small non-randomized studies, it was withdrawn from the market for commercial reasons. However, even with the PLAATO device, we discovered specific risks associated with the implantation procedure, such as device embolization and cardiac tamponade.[9,10]

Abbreviations

Atrial fibrillation (AF)
Left atrial appendage (LAA)
Direct oral anticoagulants (DOACs)
Dual antiplatelet (DAPT)
Device-related thrombosis (DRT)
Pericardial effusion (PE)
Left atrial appendage closure (LAAC)
Cerebral embolic protection (CEP)
Trans-esophageal echocardiography (TEE)
Single antiplatelet therapy (SAPT)

To date, only the WATCHMAN device has demonstrated superiority in long-term follow-up compared to chronic warfarin therapy in randomized controlled trials[11–13] and has been approved in the USA and Japan. An illustration of the WATCHMAN occluding the LAA is shown in Fig. 1. Despite being a less invasive procedure (compared to surgical LAA ligation), transcatheter left atrial appendage closure (LAAC) has been linked to potentially serious complications due to the need for a transseptal puncture, manipulation of stiff wires, guide catheters in the left atrium, and device release in the LAA. There are varied opinions regarding the anticoagulation strategy adopted following

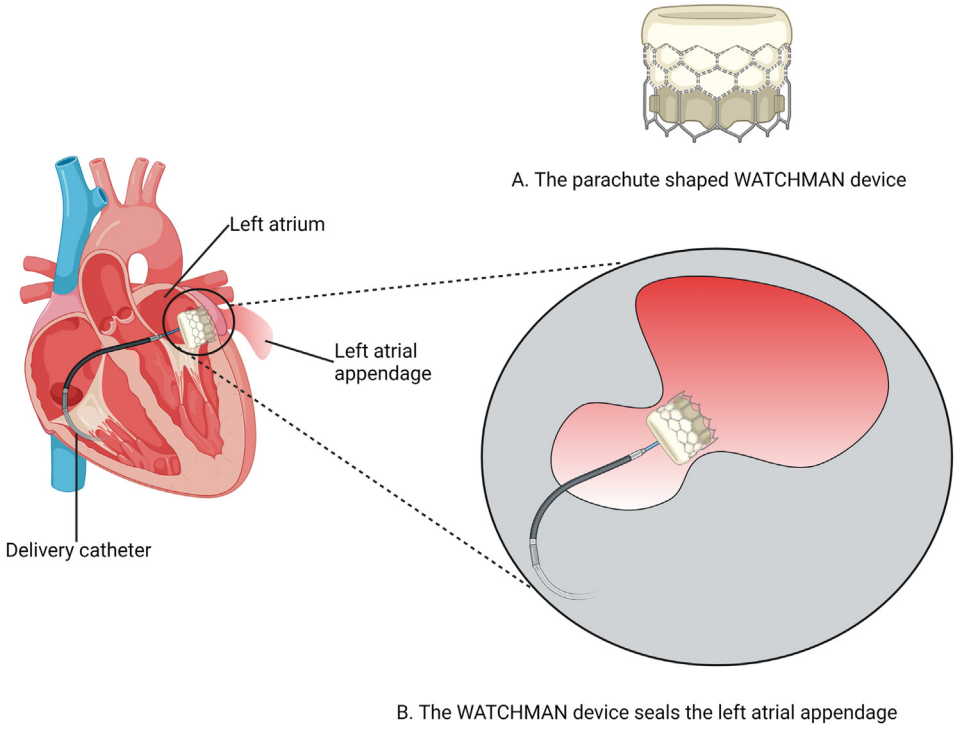

Fig. 1. Simplified illustration of the WATCHMAN device.

WATCHMAN device implantation. Hence, this review focuses on highlighting the most important complications of the WATCHMAN device in the existing literature, and discusses various anticoagulation strategies and their related challenges.

2. Methods

To summarize the body of available evidence, a scoping review design was used to incorporate a range of studies in a narrative format. For this purpose, we identified the relevant literature by performing a search of the bibliographic databases of MEDLINE and ClinicalTrials using the keywords "WATCHMAN", "stroke prophylaxis", and "complications" and "procedure outcomes".

3. Procedural complications

Although WATCHMAN devices have emerged as a promising therapy for thromboembolic prophylaxis in non-valvular atrial fibrillation (NVAF), LAAC operators must understand potential procedural pitfalls, avoid complications through careful procedural planning, and execute safe procedures. The major landmark clinical trials involving WATCHMAN devices are summarized in Table 1. Hence, the most clinically relevant complications are discussed extensively in the following sections.

3.1. Pericardial effusion

Pericardial effusion (PE) is the most common serious procedure-related complication of transcatheter LAA occlusion via the WATCHMAN device. Its incidence ranges from 0.29% to 4.8%.[14,15] Although rare, it is of great importance because LAAC might be offered to otherwise clinically asymptomatic patients. This incidence has declined with increasing numbers of implantations and improved operator training on LAAC implantation, such that later trials showed that PE declined to appropriately modest rates[16] and decreasing to zero percent in the latest PINNACLE FLX trial.[17] This might indicate that these complications are associated with the learning curve and become less frequent after experience.

Various observational studies have attempted to analyze predictors and elucidate the underlying mechanisms of PE after LAAC. Prior studies have indicated that female sex, paroxysmal AF, change in sinus rhythm, device retrieval times, and intraoperative time have a positive association with PE during the perioperative period.[18] Since percutaneous LAAC is mainly indicated for patients with

Table 1. Summary of WATCHMAN Device-related complications in landmark clinical trials.

Authors	Year	Title	Number of patients	Age	Male, %	Pericardial effusion, n (%)	Device Embolization	Major bleeding	Procedure-related ischemic stroke, n (%)
Lakkireddy et al.[20]	2021	Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE)	Watchman device = 896	75.1 ± 7.6	61.3	11 (1.22)	2 (0.22)	–	–
Reddy et al.[15]	2014	PROTECT AF Clinical Trial	n = 463	71.7 ± 8.8	70.4	22 (4.8)	3 (0.6)	22 (4.8)	6 (1.3)
Holmes et al.[13]	2014	PREVAIL Clinical Trial	n = 269	74.0 ± 7.4	67.70%	1 (0.4)	2 (0.7)	1 (0.4)	2 (0.7)
Holmes et al.[16]	2019	Continued Access to PROTECT AF (CAP) and The Continued Access to PREVAIL (CAP2) Registry	CAP = 566 CAP2 = 578	CAP = 73.96 ± 8.27 CAP2 = 75.28 ± 7.99	CAP = 65.5 CAP2 = 60.4	CAP = 7 (1.2) CAP2 = NA	CAP = 1 (0.2) CAP2 = NA	CAP = 4 (0.7) CAP = NA	CAP = 2 (0.5) CAP2 = NA
Reddy et al.[14]	2017	Post-Approval U.S. Experience with Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation	n = 3822	–	–	11 (0.29)	9 (0.24)	Not available	3 (0.078)
Kar et al.[17]	2021	PINNACLE FLX Trial	n = 400	73.8 ± 8.6	64.5	0 (0)	0 (0)	Not available	3 (0.7)

non-valvular AF and a high bleeding risk from anticoagulant therapy, these underlying conditions would make them more vulnerable to procedural complications, of which PE is the most common.

Some anatomical aspects should also be considered when examining the increased risk of PE after LAAC. Since the atrial appendage is a very thin-walled structure, the epicardium covers almost its entirety. Any attempt at LAA instrumentation by a delivery system or a closure device might result in pericardial bleeding due to local trauma and could precipitate cardiac tamponade. Additionally, other anatomically adjacent structures, such as the pulmonary veins, may be damaged during LAAC, leading to PE.

3.2. Device embolization

Device embolization occurs because of device malpositioning or inappropriate device sizing. Embolization rates range from 0.2 to 0.7 percent during LAAC closure with the WATCHMAN device. Selection of undersized devices, large LAA ostia size, short LAA length for the WATCHMAN, and unusual LAA morphologies are negative predictors of device embolization.[19] To avoid embolization, it is essential to select patients with favorable LAA morphology, and care should be taken in the selection of the appropriate device sizing during selection. Low embolization rates have been reported in recent LAAC studies and registries, which may be related to operator experience and better sizing of the LAA, for example, using a cardiac computed tomography scan.[20] Moreover, the latest PINNACLE FLX trial reported no embolization, which reflects increased operator experience, similar to lower rates of PE in recent studies.

A device-specific criteria were proposed to be checked before making the final decision to release the LAAC device. The PASS criteria are commonly used with the WATCHMAN device.[11] This implies that the Watchman-Device must be fully expanded and compressed by at least 10%−30% of its original size. If the device is too deep in the LAA and therefore not fully expanded, it must be partially recaptured and repositioned. If the device is too proximal, complete recapture and device exchange are necessary. Additionally, before releasing the device, a "tug-test" should be performed in all cases to confirm a secure position within the LAA.

3.3. Procedure-related ischemic stroke

Since the primary purpose of the LAAC procedure via the WATCHMAN device is stroke prophylaxis, the reduction of procedural thromboembolic risk is critical. Procedural stroke rates of approximately around 1% are noted across a range of studies and have not changed significantly over time.[13,15,16] Although the exact mechanism is unknown, several causes can be identified. First, during manipulation of the delivery system and device, a thrombus in the left atrium or its appendage can be dislodged, causing ischemic stroke. Hence, it is strongly suggested to screen for thrombi via echocardiography before performing transseptal puncture. Furthermore, heparin administration with an initial dose of 100 IU/kg and a target procedural activated clotting time of greater than 250 s is recommended to reduce the risk of thrombus formation. A portion of this heparin dose can be administered before transseptal puncture.

It might be possible to use a cerebral embolic protection (CEP) device during LAAC because of the documented rate of periprocedural stroke. Although the stroke risk in LAAC is similar to Trans-Aortic Valve replacement (0.5%−1.2%), there remains a relatively low uptake of CEP with LAAC procedures.[21,22] The lack of robust evidence in the setting of LAAC is most likely to blame the reluctance to use CEP. However, few studies have indicated that this approach is feasible.[23]

3.4. Device-related thrombus formation

Thrombus formation is a potentially serious complication of LAAC via the WATCHMAN device, particularly just after implantation before endothelialization of the device. The incidence rates of thrombus formation have varied in previous studies.[15,24] According to the existing literature, a few risk factors for device-related thrombus formation include higher CHADS2/CHA2DS2-VASc scores, lower ejection fraction, deeper device implantation, and incomplete occlusion of the LAA.[13,25] Recent studies have shown that a large LAA width is a significant predictor of device-related thrombus in cases where the WATCHMAN device is used.[26] Hence, to reduce the risk of thrombus formation, the appropriate closure device size should be carefully selected, particularly in the case of a large LAA, while attempting to avoid deep implantation and a large gap between the pulmonary valve ridge and device.

Although the optimal antithrombotic therapy for preventing device-related thrombosis (DRT) is unclear, a recent propensity score matching study for WATCHMAN found that initial oral anticoagulant (OAC) therapy is associated with a lower rate of DRT than antiplatelet therapy.[27] Similarly, there is

currently no consensus on device-related thrombus management strategies. However, in clinical practice, anticoagulation with OAC or low-molecular-weight heparin can be used as first-line therapy. Although the treatment duration varied significantly, with a minimum of 2 weeks and a maximum of 6 months, these strategies resulted in complete thrombus resolution in 95 percent of cases.[28]

4. The rationale for antithrombotic therapy

The WATCHMAN device is safe and effective in preventing stroke and systemic embolization in the population of interest in this review; however, it does not eliminate the need for short-term antithrombotic therapy in the post-procedural period, as it is essential to prevent DRT formation until complete device endothelialization.[29]

In a recent meta-analysis that included 12,000 patients undergoing LAAC implantation, the absolute risk of DRT was estimated to be only 3.8%. However, DRT is not inconsequential, as it is associated with a four-fold higher risk of ischemic events.[30] Therefore, proper postprocedural management is crucial for the long-term benefits of a nonpharmacological stroke prevention strategy. Unfortunately, there is no consensus on the optimal post-implant therapy, yet many variables, including significant inter-individual variability, play a major role in the healing process.

4.1. Histopathology and endothelization[31]

The healing mechanism of the Watchman device is still not fully understood, as there is a lack of detailed histopathological data regarding the endothelization process in humans. Based on a study investigating the healing process with WATCHMAN in nine dogs that were euthanized at 3-time points, it was found that a thin layer of fibrin covering the device appeared by day 3, and by day 45, the device developed an organized neo-endocardial atrial surface. By day 90, fibrous tissue with a monolayer of endothelial-like cells appeared on this neo-endocardium, and endothelization appeared to be completed in dog models. Similar findings were observed in the hearts of patients who died on different post-implantation days due to non-device-related causes.[32] Another study found that at 28 days, the atrial surface of WATCHMAN was completely covered by neo-endocardial tissue.[33] However, owing to many inter-individual variables, this timeline could be different for humans.

A case report of a 74-year-old man affected by Rendu Osler Weber syndrome is worthy of mention, as it showed a 10month post-implantation delay in incomplete endothelization in explanted WATCHMAN, raising caution that the duration of antithrombotic therapy should be individualized and monitored.[34]

4.2. Major WATCHMAN trails

Trials such as PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), PREVAIL (Watchman LAAC Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), CAP (Continued Access to PROTECT-AF), CAP2 (Continued Access to PREVAIL), ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology), and EWOLUTION (Registry on WATCHMAN Outcomes in Real-Life Utilization) laid the foundations of post-operative WATCHMAN therapy and management. They had similar primary endpoints, that is, to check the safety and efficacy of the WATCHMAN device compared to NVAF medical management, but at the same time targeted various subpopulations with different bleeding susceptibilities.

4.3. PROTECT-AF and PREVAIL trials[11,13]

PROTECT AF is a pivotal multicenter non-inferiority RCT trial conducted on 707 NVAF patients with a CHADS2VASC score $\geq$1 to assess the efficacy and safety of the WATCHMAN device compared with warfarin. The PREVAIL trial,[13] a non-inferiority intention-to-treat prospective randomized trial, addressed the limitations of the PROTECT AF study.

Postoperatively, warfarin was continued for approximately 45 days, followed by clopidogrel for 4.5 months and lifelong aspirin. This largely empirical regime was intended to provide antithrombotic coverage until endothelization was completed and was partially supported by preclinical dog studies that showed complete endocardial coverage of WATCHMAN with warfarin at 45 days.[32] Both trials demonstrated the superiority of LAAC using the WATCHMAN device for stroke and embolization prevention; however, they only included patients eligible for six weeks of warfarin post-implantation.

4.4. ASAP trail[35]

ASAP is a multicenter, prospective, non-randomized study addressing a population with an elevated risk of bleeding and absolute contraindication to

warfarin (n = 150) and eligible for 6-month antiplatelet treatment post-WATCHMAN device implant followed by lifelong aspirin.

Follow-up ranged from to 3–24 months and consisted of transesophageal echocardiography (TEE) at 3 and 12 months to check for DRT formation and peri-device LAA flow. The ASAP registry showed a DRT incidence of 4.0% and a thromboembolic event rate of 2.3% per year. Additionally, the annualized ischemic stroke rate was much lower than that expected in patients treated with aspirin alone.[35,36] This study demonstrated that the Watchman device can be safely used in high stroke risk patients with contraindications to systemic oral anticoagulation.

4.5. EWOLUTION trial[24,37]

EWOLUTION is a non-randomized multicenter prospective cohort study, with over 1000 patients at high risk for thromboembolism and bleeding; of whom 62% are ineligible for OAT by their physician due to poor compliance, comorbidities, and bleeding history.

Follow-up generally consisted of a clinical visit between 1- and 3-months post-procedure, LAA imaging to access peridevice flow, and annual visits. Anticoagulation therapy included warfarin, direct oral anticoagulants (DOACs), DAPT, single antiplatelet therapy (SAPT), and no anticoagulation in 16%, 11%, 60%, 7%, and 6% respectively. The trial concluded that the risks of DRT, ischemic stroke, and systemic embolization were statistically nonsignificant between different cohorts.

4.6. Post-WATCHMAN implantation therapy

The debate regarding the optimal post-WATCHMAN implantation regimen remains open. A multitude of variables, including the patient's bleeding risk, physician's choice, contradictions to DOAC, and history of stroke, play a vital role in therapeutic management, duration, and follow-up strategies.[31]

Based on current knowledge, in patients without relative and/or absolute contraindications to warfarin for a short duration, the optimal regimen post-WATCHMAN implantation should be warfarin (INR 2.0–3.0) and aspirin (81 mg) followed by TEE on day 45. If TEE shows minimal residual peridevice flow (≤5 mm) and no device-related thrombus, indicative of a successful LAAC, warfarin should be discontinued. This should be followed by DAPT with clopidogrel (75 mg) and aspirin (81–325 mg) for six months and TEE. Based on the 6-month TEE results, DAPT can be switched to SAPT with aspirin (325 mg).[11,29,31,38] The appropriate course of action for DRT seen in TEE will be discussed later.

Due to limited data, a post-WATCHMAN implantation regimen is yet to be agreed upon. However, many studies focusing on different stages of treatment, alternative drugs, and their short- and long-term effects have recently appeared. These provide alternate anticoagulation regimens designed especially for individuals with a very high bleeding risk, contraindications to warfarin, and/or systemic anticoagulation.

4.7. DAPT/DOAC without warfarin transition

As PROTECT-AF and PREVAIL were designed before the widespread use of DOAC agents and they only included patients' eligible for warfarin after implantation, the ASAP trial was the first major study targeting a population with contraindications for oral anticoagulants, namely warfarin. As warfarin use has several limitations, including a narrow therapeutic window, the need for regular blood tests, drug–drug interactions, and interpersonal drug response variability, patient management with warfarin is difficult. The ASAP study concluded that LAAC with the Watchman device can be safely performed without requiring warfarin transition in the early period and is a viable alternative for patients at high risk for stroke but with contraindications to systemic oral anticoagulation.[35] Also, patients from EWOLUTION registry receiving DOAC treatment (dabigatran, rivaroxaban, and apixaban) after LAAC suggested that it was a safe option for patients with warfarin contraindications, as DRT irate was only 1.3%.[39] Fig. 2 highlights the treatment post-WATCHMAN in patients without contraindications to OACs.

The results from multiple trials demonstrated that neither DAPT nor DOAC treatment is inferior to warfarin in terms of stroke or bleeding risk, and the major nonprocedural bleeding rate was 2.7%, with a relative risk reduction of 46% when compared to warfarin. Additionally, no significant difference was found in DRT incidence, annual rate of ischemic stroke, or systemic embolization related to the presence of DRT between the two regimens.[24,31,40,41]

4.8. NOAC and SAPT vs OAC/DOAC alone[42]

A single-center retrospective study with a relatively small sample size (160 patients) and a short follow-up time compared two cohorts with different postoperative regimens. One consisted of a single OAC/direct OAC (DOAC) therapy with warfarin (INR maintained at 2–3), rivaroxaban (15 mg), or

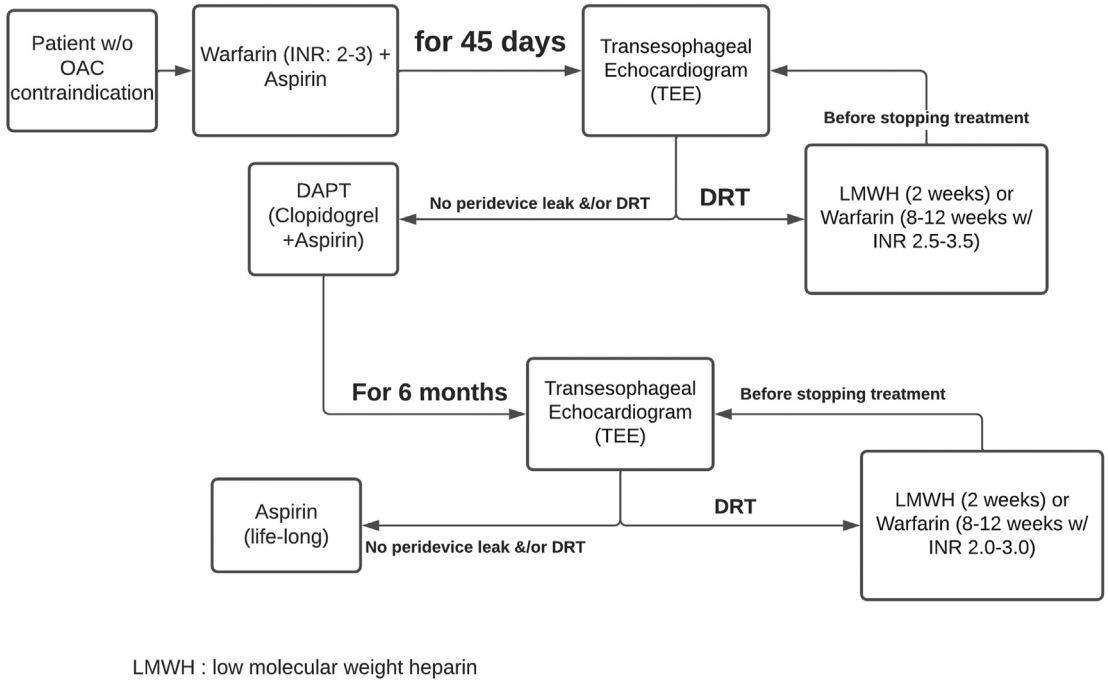

Fig. 2. Post-WATCHMAN treatment in patients without contraindication to oral anticoagulation.

dabigatran (220 mg), and the other consisted of a single antiplatelet medication to OAC/DOAC. Specifically, DOAC + SAPT therapy included rivaroxaban (15 mg), aspirin (0.1 g), clopidogrel (75 mg), dabigatran (220 mg), and aspirin (0.1 g)/ clopidogrel (75 mg).

Imaging studies were conducted after three months. If TEE showed no DRT or minimal peri-device flow, these two regimens were followed for 3 months with aspirin (0.1 g) and clopidogrel (75 mg) for 3 months, followed by aspirin (0.1 g) or clopidogrel (75 mg) indefinitely.

The results showed no significant difference in the incidence of ischemic stroke, major bleeding events, or all-cause mortality between the two cohorts during the postoperative follow-up period. However, the OAC/DOAC-only group was associated with a higher incidence of early DRT.

In conclusion, it was also demonstrated that NOAC + SAPT therapy was safe and effective in short-term follow-up and was associated with lower early DRT formation.[42]

4.9. APT VS OAC[27]

The safety and efficacy of OAC and antiplatelet treatment were compared in a propensity-matched study that included patients from various registries who underwent LAAC with the WATCHMAN device and received either OAC or APT post-implantation.[11–13,15] They were matched and compared for nonprocedural bleeding, stroke, or systemic thromboembolism over 6 months. The OAC cohort had 95% receiving warfarin and 5% receiving non-warfarin OAC over 45 days post-implantation, and the majority also received SAPT, followed by 6-month single or DAPT therapy. In the APT cohort, 91% received DAPT and 9% received SAPT for variable durations.

The study demonstrated that freedom from thromboembolism beyond 7 days and six-month freedom from nonprocedural major bleeding and stroke were similar in the two cohorts despite a large number of early bleeds with OAC. Notably, DRT was significantly more frequent with APT alone. Therefore, to avoid such complications, a valid option is to continue OAC until efficient closure has been confirmed on TEE in patients with no contraindications, whereas patients with strong contraindications for OAC and APT should be immediately started after LAAC, and it is a reasonable alternative in patients with a very high bleeding risk. Furthermore, a study also showed that in real-world LAAC registries, DAPT and DOAC may have similar safety and DRT occurrence compared to warfarin and aspirin therapy.[31]

4.10. DAOC vs warfarin

In A multicenter retrospective analysis comparing 212 patients receiving warfarin and 214 patients receiving DOAC (apixaban 46%, rivaroxaban 46%,

dabigatran 7%, and edoxaban 1%) it was shown that peri- and post-procedural DOAC administration was a safe substitute for warfarin without an absolute increase in the risk of bleeding. CT or TEE follow-up at 6 weeks and four months CT or TEE follow-up showed that the DRT rate and thromboembolic events were comparable between groups.[43]

Furthermore, another smaller study concluded that DOACs are safe and effective, especially during the first 45 days after device implantation.[44] However, a prospective cohort study comparing dabigatran (a direct thrombin inhibitor) to rivaroxaban (a selective Xa inhibitor) reported that not all DOAC have similar safety profiles. During the 3-month TEE follow-up period, a markedly increased incidence of DRT with a higher average length and width of DRT was observed in the dabigatran cohort, suggesting that it might decrease endothelialization and increase platelet activity, which may serve as an independent factor for thrombus formation.[45,46]

No substantial differences in terms of bleeding events and incidence of systemic thromboembolism, including stroke and cardiac embolism, were observed between cohorts.[45,47] Furthermore, other studies also provided definitive evidence on the clinical benefit of rivaroxaban for post-anticoagulation of LAAC and proved its superiority over warfarin in the resolution of LAA thrombi in NVAF.[43,48,49] However, larger randomized controlled trials are needed to validate the non-inferiority of DOAC over warfarin for LAAC.[37,50]

4.11. Device related thrombosis sequela

After WATCHMAN device implantation, endothelialization occurs, which is similar to the local response to tissue injury, and can lead to thrombus formation. Therefore, active postoperative antithrombotic therapy is required to prevent DRT.[51]

The direct association between DRT and an increased risk of stroke, transient ischemic attack, or systemic embolization is still open to debate. In a retrospective analysis of PROTECT-AF, PREVAIL, CAP, and CAP2 registries, DRT was associated with a higher rate of stroke and systemic embolism,[51,52] but the EWOLUTION study suggested otherwise.[40] A limitation of these analyses is the fact that DRT diagnosis itself proves to be difficult on TEE, and none of these registries provided a standardized definition of DRT. Additionally, the frequency and timing of TEE in identifying DRT were not uniform among these trials. Notably, a recent study suggested that DRT is an independent predictor of stroke and TIA post-LAAC-implantation.[52]

4.12. Treatment of device-related thrombosis

The most common and effective treatment for DRT, when detected on TEE or computed tomographic angiographic imaging, is low–molecular weight heparin (LMWH) and OAC agents (mainly warfarin). LMWH is the preferred treatment for large and/or mobile thrombi (>15 mm). In a 2019 study, the average duration of LMWH treatment was two weeks, which proved to be highly effective, with a thrombus resolution rate of 100%.[31]

In the case of warfarin, 8–12 weeks of therapy (aiming for INR 2–3) in patients previously without OAC at the time of DRT diagnosis is required. Otherwise, OAC treatment should be intensified, and INR should be kept to 2.5–3.5 Rarely, surgical removal of the thrombus and/or LAA device may be required in cases such as large thrombi, recurrent device-related embolization, or failure of OAC treatment.[53] There are sparse data on DOAC therapy for DRT treatment with dabigatran and apixaban, which have been shown to be effective in some cases.[54–56] In all cases, imaging examinations should be performed before stopping antithrombotic treatment, and delayed imaging at 3–6 months should be considered to investigate recurrence.

4.13. Bleeding outcomes

Despite being an excellent choice to reduce thromboembolic risk post-WATCHMAN device implantation, bleeding is a major complication of oral anticoagulation. A recent pooled analysis of the PROTEC-AF and PREVAIL trials showed no difference between LAAC and long-term warfarin at a three-year follow-up in terms of primary bleeding events. However, after cessation of OAC/DOAC/DAPT therapy in the post-implantation period, LAAC resulted in a significant reduction in major bleeding events. The analysis also showed that despite a significant procedural hazard, in the long term, LAAC is associated with 72% relative risk reduction in major bleeding events compared with long-term warfarin therapy.[57]

4.14. Imaging and management

TEE is the gold standard to confirm device failure.[29,58,59] The United States Food and Drug Administration label for WATCHMAN requires TEE imaging at days 45 and 12-months post-LAAC. The first surveillance imaging should preferably be performed after the stepdown of antithrombotic therapy (cessation of OAC/DOAC/DAPT therapy)

to allow better detection of DRT.[31] In most clinical settings, however, TEE imaging is performed at 6–12 weeks and is repeated only in cases of abnormal findings (significant residual leaks >3–5 mm, DRT, or device dispositioning).[28] In the case of significant postprocedural leaks (>5 mm), DAPT with aspirin and clopidogrel is recommended, and imaging should be repeated after 3 months. Small residual leaks (<5 mm) are considered irrelevant as they may close spontaneously, and their presence has not been linked to an increased risk of thromboembolism compared with complete LAAO closure.[60]

Furthermore, in potential high-risk patients for thrombus formation, such as left ventricular ejection fraction <40%, hematological abnormalities, high CHA2DS2VASc score, residual leak, etc., it is advised to perform additional imaging at 6–12 months.[31] Considering the invasive nature of TEE, noninvasive imaging techniques, such as cardiac computed tomography angiography, are also gaining popularity to assess adequate left LAAC and for proper DRT monitoring. However, due to a lack of standardized definition of DRT on computed tomography angiography for WATCHMAN, guidelines are still in development, and additional studies are needed to determine standardized parameters for DRT diagnosis.[61] Additional use of serum biomarkers, such as the level of prothrombin fragments 1 + 2 and D-dimer, could be viable options and may potentially help us better understand and manage the post-WATCHMAN device implantation healing process. However, the relationship between these parameters and imaging-confirmed DRT is yet to be validated.

5. Conclusion

In conclusion, the WATCHMAN device could serve as an attractive and safe procedure for percutaneous closure of the left atrial appendage owing to its low rate of complications. However, future research is warranted on the long-term outcomes of this procedure as well as the optimization of post-procedural anticoagulant therapy.

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Ethics statement

As no human research was conducted in this review, and no data sets were generated; therefore, no ethical approval was required.

Conflict of interest

Authors declare no competing interests.

References

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int J Stroke*. 2021;16(2):217–221.
2. Wang G, Joo H, Tong X, George MG. Hospital costs associated with atrial fibrillation for patients with ischemic stroke aged 18-64 years in the United States. *Stroke*. 2015;46(5):1314–1320.
3. Kirshner HS. Differentiating ischemic stroke subtypes: risk factors and secondary prevention. *J Neurol Sci*. 2009;279(1–2):1–8.
4. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61(2):755–759.
5. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115(21):2689–2696.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151.
7. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.
9. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multicenter feasibility trials. *J Am Coll Cardiol*. 2005;46(1):9–14.
10. Ussia GP, Mule M, Cammalleri V, et al. Percutaneous closure of left atrial appendage to prevent embolic events in high-risk patients with chronic atrial fibrillation. *Cathet Cardiovasc Interv*. 2009;74(2):217–222.
11. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374(9689):534–542.
12. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. *Circulation*. 2013;127(6):720–729.
13. Holmes Jr DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64(1):1–12.
14. Reddy VY, Gibson DN, Kar S, et al. Post-approval U.S. Experience with left atrial appendage closure for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2017;69(3):253–261.
15. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312(19):1988–1998.
16. Holmes Jr DR, Reddy VY, Gordon NT, et al. Long-term safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol*. 2019;74(23):2878–2889.
17. Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation*. 2021;143(18):1754–1762.

18. Yang L, Zhang X, Jin Q, et al. Pericardial effusion during the perioperative period for left atrial appendage closure. *Front Cardiovasc Med*. 2021;8, 678460.
19. Jazayeri MA, Vuddanda V, Parikh V, Lakkireddy DR. Percutaneous left atrial appendage closure: current state of the art. *Curr Opin Cardiol*. 2017;32(1):27−38.
20. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer amulet left atrial appendage occluder versus watchman device for stroke prophylaxis (amulet ide): a randomized, controlled trial. *Circulation*. 2021;144(19):1543−1552.
21. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380(18):1706−1715.
22. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695−1705.
23. Meincke F, Spangenberg T, Kreidel F, et al. Rationale of cerebral protection devices in left atrial appendage occlusion. *Cathet Cardiovasc Interv*. 2017;89(1):154−158.
24. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 2017;14(9):1302−1308.
25. Saw J, Tzikas A, Shakir S, et al. Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the amplatzer cardiac Plug. *JACC Cardiovasc Interv*. 2017;10(4):391−399.
26. Plicht B, Konorza TF, Kahlert P, et al. Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion. *JACC Cardiovasc Interv*. 2013;6(6):606−613.
27. Sondergaard L, Wong YH, Reddy VY, et al. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with WATCHMAN. *JACC Cardiovasc Interv*. 2019;12(11):1055−1063.
28. Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. *Cathet Cardiovasc Interv*. 2017;90(5):E111−E121.
29. Casu G, Gulizia MM, Molon G, et al. ANMCO/AIAC/SICI-GISE/SIC/SICCH Consensus Document: percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation patients: indications, patient selection, staff skills, organisation, and training. *Eur Heart J Suppl*. 2017;19(Suppl D):D333−D353.
30. Alkhouli M, Busu T, Shah K, Osman M, Alqahtani F, Raybuck B. Incidence and clinical impact of device-related thrombus following percutaneous left atrial appendage occlusion: a meta-analysis. *JACC Clin Electrophysiol*. 2018;4(12):1629−1637.
31. Saw J, Nielsen-Kudsk JE, Bergmann M, et al. Antithrombotic therapy and device-related thrombosis following endovascular left atrial appendage closure. *JACC Cardiovasc Interv*. 2019;12(11):1067−1076.
32. Schwartz RS, Holmes DR, Van Tassel RA, et al. Left atrial appendage obliteration: mechanisms of healing and intracardiac integration. *JACC Cardiovasc Interv*. 2010;3(8):870−877.
33. Kar S, Hou D, Jones R, et al. Impact of Watchman and Amplatzer devices on left atrial appendage adjacent structures and healing response in a canine model. *JACC Cardiovasc Interv*. 2014;7(7):801−809.
34. Massarenti L, Yilmaz A. Incomplete endothelialization of left atrial appendage occlusion device 10 months after implantation. *J Cardiovasc Electrophysiol*. 2012;23(12):1384−1385.
35. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix feasibility study with watchman left atrial appendage closure Technology). *J Am Coll Cardiol*. 2013;61(25):2551−2556.
36. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110(16):2287−2292.
37. Cohen JA, Heist EK, Galvin J, et al. A comparison of post-procedural anticoagulation in high-risk patients undergoing WATCHMAN device implantation. *Pacing Clin Electrophysiol*. 2019;42(10):1304−1309.
38. Magdi M, Renjithal SLM, Mubasher M, et al. The WATCHMAN device and post-implantation anticoagulation management. A review of key studies and the risk of device-related thrombosis. *Am J Cardiovasc Dis*. 2021;11(6):714−722.
39. Bergmann MW, Betts TR, Sievert H, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention*. 2017;13(7):877−884.
40. Boersma LV, Ince H, Kische S, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure Technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol*. 2019;12(4), e006841.
41. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of WATCHMAN LAA closure at one year in patients on dual antiplatelet therapy: results of the DAPT subgroup from the EWOLUTION all-comers study. *EuroIntervention*. 2018;13(17):2003−2011.
42. Li W, Gao R, Zhao J, et al. Safety and efficacy of different anticoagulation regimens after left atrial appendage occlusion. *Ann Palliat Med*. 2022;11(1):201−209.
43. Enomoto Y, Gadiyaram VK, Gianni C, et al. Use of non-warfarin oral anticoagulants instead of warfarin during left atrial appendage closure with the Watchman device. *Heart Rhythm*. 2017;14(1):19−24.
44. Bosche LI, Afshari F, Schone D, Ewers A, Mugge A, Gotzmann M. Initial experience with novel oral anticoagulants during the first 45 Days after left atrial appendage closure with the watchman device. *Clin Cardiol*. 2015;38(12):720−724.
45. Li X, Zhang X, Jin Q, et al. Clinical efficacy and safety comparison of rivaroxaban and dabigatran for nonvalvular atrial fibrillation patients undergoing percutaneous left atrial appendage closure operation. *Front Pharmacol*. 2021;12, 614762.
46. Li X, Zhang X, Jin Q, et al. The impact of dabigatran and rivaroxaban on variation of platelet activation biomarkers and DRT following percutaneous left atrial appendage closure. *Front Pharmacol*. 2021;12, 723905.
47. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *Chest*. 2016;150(6):1302−1312.
48. Ke HH, He Y, Lv XW, Zhang EH, Wei Z, Li JY. Efficacy and safety of rivaroxaban on the resolution of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation patients. *J Thromb Thrombolysis*. 2019;48(2):270−276.
49. 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;13(7), e008481.
50. Fry E, Bollempali H, Suarez K, Banchs J, Michel J. Watchman outcomes comparing post-implantation anticoagulation with warfarin versus direct oral anticoagulants. *J Intervent Card Electrophysiol*. 2021;61(1):137−144.
51. Dukkipati SR, Kar S, Holmes DR, et al. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. *Circulation*. 2018;138(9):874−885.
52. Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol*. 2018;71(14):1528−1536.

53. Lammers J, Elenbaas T, Meijer A. Thrombus formation on an Amplatzer closure device after left atrial appendage closure. *Eur Heart J*. 2013;34(10):741.
54. Ciconte G, Conti M, Baldi M, Saviano M, Vicedomini G, Pappone C. Thrombosis on a left atrial appendage occluder device: the double-edged sword of stroke prevention strategies in atrial fibrillation. *J Cardiovasc Med*. 2017;18(11): 920−921.
55. Freixa X, Scalone G, Martin-Yuste V, Vidal B. Large protruding thrombus over left atrial appendage occlusion device successfully treated with apixaban. *Eur Heart J*. 2015;36(23): 1427.
56. Ketterer U, D'Ancona G, Siegel I, Ortak J, Ince H, Kische S. Percutaneous left atrial appendage occlusion: device thrombosis in clopidogrel non-responders. *Int J Cardiol*. 2016;204: 196−197.
57. 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(15):1925−1932.
58. Alli O, Holmes Jr D. Left atrial appendage occlusion. *Heart*. 2015;101(11):834−841.
59. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol*. 2008;52(11):924−929.
60. Berti S, Themistoclakis S, Santoro G, et al. [GISE/AIAC position paper on percutaneous left atrial appendage occlusion in patients with nonvalvular atrial fibrillation: recommendations for patient selection, facilities, competences, organizing and training requirements]. *G Ital Cardiol*. 2014;15(9):508−519.
61. Miller T, Hana D, Patibandla S, et al. Cardiac computed tomography angiography for device-related thrombus assessment after WATCHMAN FLX™ occluder device implantation: a single-center retrospective observational study. *Cardiovasc Revasc Med.* 2022;41:35−46. https://doi.org/10.1016/j.carrev.2022.01.028. Epub 2022 Feb 3. PMID: 35140053.