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Left Atrial Appendage Occlusion: Current Landscape and Future Direction

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Introduction

Stroke is a major issue in the management of nonvalvular atrial fibrillation (NVAF). Although oral anticoagulants (OACs) are an effective therapy for preventing stroke, they increase the risk of bleeding, which may not be a suitable option for some patients. Patient adherence is another concern with using OACs. Different studies have shown a nonadherence rate of 30% to 50% for OACs among patients with AF.[1]

Left atrial appendage occlusion (LAAO) is a nonpharmacologic approach to preventing stroke that seals off the LAA as the main source of thrombus formation in NVAF.[2] The WATCHMAN device (Boston Scientific Corporation) and the Amplatzer Amulet device (Abbott Structural Heart) are approved by the US Food and Drug Administration for LAAO, and continuous research studies advance clinical knowledge about these devices' safety, reliability, and effectiveness compared with OACs.[3] This study reviews notable WATCHMAN and Amulet studies.

PROTECT AF Study

The WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF) study (ClinicalTrials.gov identifier NCT00129545) was a randomized controlled trial that compared the WATCHMAN device with warfarin therapy. The primary efficacy end point was a composite of stroke, systemic embolism, and cardiovascular death. The primary safety end points were device embolization that required retrieval, pericardial effusion that required intervention, intracranial or gastrointestinal bleeding, or any bleeding that required transfusion. The trial enrolled 707 patients at 59 centers, with 463 patients randomly assigned to the device group and 244 to the warfarin group. The mean follow-up duration was 3.8 years (range, 0-6.5 years).

The study demonstrated the noninferiority of the WATCHMAN device to warfarin for the primary efficacy end point. The device group had a rate of 2.3 events per 100 patient-years compared with 3.8 events per 100 patient-years in the warfarin group (rate ratio, 0.60 [95% credible interval, 0.41-1.05]). The device also showed superiority in reducing cardiovascular mortality (1.0 events per 100 patient-years vs 2.4 events per 100 patient-years; hazard ratio, 0.40 [95% CI, 0.21-0.75]; $P = .005$) and all-cause mortality (3.2 events per 100 patient-years vs 4.8 events per 100 patient-years; hazard ratio, 0.66 [95% CI, 0.45-0.98]; $P = .04$).

The safety profile was similar between the 2 groups, with a rate of 3.6 events per 100 patient-years in the device group and 3.1 events per 100 patient-years in the warfarin group (rate ratio, 1.17 [95% CI, 0.78-1.95]). The most frequent adverse events were serious pericardial effusions in the device group and major bleeding in the warfarin group.[4]

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The PREVAIL Study

The Evaluation of the WATCHMAN Left Atrial Appendage (LAA) Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study (ClinicalTrials.gov identifier NCT01182441) was a multicenter randomized trial to investigate the efficacy of treating LAAO with the WATCHMAN device as an alternative to warfarin to prevent stroke in patients with NVAF. This study evaluated cardiovascular and unexplained death, stroke, or systemic embolism at 18 months and stroke or systemic embolism after 7 days to 18 months among 407 patients. The PREVAIL study showed LAAO noninferiority for preventing stroke or systemic embolism from 7 days to 18 months compared with warfarin, but noninferiority for the end point of cardiovascular and unexplained death, stroke, or systemic embolism at 18 months was not observed. Device-related complications were reduced compared with the earlier PROTECT AF trial.[5]

The EWOLUTION Study

This multicenter, prospective, nonrandomized cohort study enrolled 1025 patients scheduled for a WATCHMAN implantation across 47 centers in 13 countries. The Registry on WATCHMAN Outcomes in Real-Life Utilization (EWOLUTION) study (ClinicalTrials.gov identifier NCT01972282) aimed to gather data on procedural success, complications, and long-term patient outcomes, including bleeding and the incidence of stroke or transient ischemic attack (TIA). Notably, 73% of the patients were deemed unsuitable for OACs, emphasizing the device's potential in this high-risk population.

The EWOLUTION trial reported a high implantation success rate of 98.5%, with successful implantation in 1005 of 1020 patients. The rate of periprocedural serious adverse events within the first 7 days was 2.8%, including 4 deaths (1 because of a cerebral air embolism and 3 unrelated to the device or procedure). No procedural stroke, systemic embolism, or myocardial infarction events were reported.

At 1-year follow-up, the ischemic stroke rate was remarkably low, at 1.1%, translating to an 84% risk reduction compared with the expected rate without anticoagulation. The major bleeding rate was 2.6% and predominantly not related to the procedure or the device, further demonstrating a favorable safety profile. Device-associated thrombus was observed in 28 (3.7%) patients on routine transesophageal echocardiography (TEE) and was not correlated with the drug regimen.

The study concluded that LAAO closure with the WATCHMAN device has high rates of implantation and sealing success. This method of stroke risk reduction appears to be safe and effective, with an ischemic stroke rate as low as 1.1%, even though 73% of patients had a contraindication to and were not using OACs.[6]

Abbreviations

Amulet IDE, AMPLATZER™ Amulet™ LAA Occluder Trial
EWOLUTION, Registry on WATCHMAN Outcomes in Real-Life Utilization
LAAO, left atrial appendage occlusion
NVAF, nonvalvular atrial fibrillation
OAC, oral anticoagulant
PINNACLE FLX, Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology
PREVAIL, Evaluation of the WATCHMAN Left Atrial Appendage (LAA) Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
PROTECT AF, WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation
TEE, transesophageal echocardiography
TIA, transient ischemic attack

The Amplatzer Cardiac Plug Study

This large, multicenter, all-comers study evaluated the safety and efficacy of LAAO with the Amplatzer Cardiac Plug (Abbott Cardiovascular) in a real-world patient population. The study included 1047 patients with NVAF who underwent LAAO with the Amplatzer Cardiac Plug across 22 centers. The primary end point was device efficacy to prevent stroke, TIA, and systemic embolism, assessed by comparing the actual event rate at follow-up with the predicted event rate by the Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category (CHA_2DS_2-VASc) score.

The study showcased a high procedural success rate of 97.3%. Periprocedural adverse events occurred in 4.97% of patients, with the most common being cardiac tamponade, major bleeding, and stroke. Follow-up was complete in 98.2% of successfully implanted patients, with an average follow-up of 13 months.

The annual rate of systemic thromboembolism was 2.3%, representing a 59.1% risk reduction compared with the predicted rate. The annual rate of major bleeding was 2.1%, a 61.0% risk reduction. Subgroup analyses showed that patients with single LAAO on aspirin monotherapy or no therapy and longer follow-up had fewer cerebral and bleeding events.[7]

The PINNACLE FLX Study

The Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology (PINNACLE FLX) study (ClinicalTrials.gov identifier NCT02702271) was a prospective, single-arm study that evaluated the safety and efficacy of WATCHMAN FLX LAAO Closure Technology (Boston Scientific Corporation) in patients with NVAF suitable for short-term OACs. A total of 400 patients (67% female) at 29 US sites were enrolled. The primary safety end point was a composite of all-cause death, ischemic stroke (including TIA), systemic embolism, and device-related or procedure-related events requiring open cardiac surgery or major endovascular intervention within 7 days after procedure or by hospital discharge. The prespecified primary effectiveness end point was the rate of successful LAA closure (peridevice flow <5 mm) at 12 months by TEE. The study also showed a high rate of OAC discontinuation (96.3%) at 45-day follow-up, which supports the device's potential to facilitate early cessation of anticoagulation therapy.

The rate of events for the primary safety end point was 0.5%. The primary efficacy end point was 100%, and all patients had successful LAA closure at 12 months.

This study's findings confirmed the safety and efficacy of the WATCHMAN FLX device in patients with NVAF suitable for short-duration OAC use. With its high rates of successful LAA closure, minimal complications, and facilitation of early OAC discontinuation, the WATCHMAN FLX device becomes a promising alternative to long-term anticoagulation in such patients.[8]

European Experience With WATCHMAN FLX Device

The FLXibility postapproval study was a single-center, prospective study conducted at Aarhus University Hospital in Aarhus, Denmark. The main purpose of this study was to evaluate the WATCHMAN FLX device's performance in the real world and the feasibility of intracardiac echocardiography–guided implantation during LAAO procedures. From March 2019 to January 2020, 91 consecutive patients were implanted with the WATCHMAN FLX device. The primary outcomes of interest were the technical and procedural success of the LAAO procedure.

This study showed a technical success rate of 99%, and the WATCHMAN FLX device was successfully implanted in 90 patients. The procedural success rate was equally high, at 93.4%. The median procedure time was 38 minutes, which showed no significant difference in the TEE-guided and intracardiac echocardiography–guided procedures. Periprocedural complications occurred in 5.5% of patients, with pericardial effusion being the predominant complication, reported in 2.2% of patients. The device closure rate was 96.7% on follow-up, and only a 3.3% rate of peridevice leak was seen on TEE images. There were no thromboses related to the devices. From the end of the procedure to the 8-week follow-up, there was a significant reduction in the mean device compression rate, reflecting the shaping of LAA around the device over time.[9]

The SURPASS Trial

The SURPASS trial directly compared the WATCHMAN and WATCHMAN FLX devices within the National Cardiovascular Data Registry LAAO Registry. The primary safety end point evaluated in the SURPASS analysis was the occurrence of a composite of adverse events, including all-cause death, ischemic stroke, systemic embolism, or device-related or procedure-related complications necessitating open cardiac surgery or major endovascular intervention. This composite end point was assessed within 7 days of the procedure or until hospital discharge, whichever occurred later. The study also tracked the rate of ischemic stroke at 1 year as a key efficacy end point. The study demonstrated comparable safety and efficacy profiles between the

2 devices. The WATCHMAN FLX showed superior LAAO rates (98.1% vs 96.2%) but a slightly higher incidence of device-related complications (7.1% vs 4.0%).[10]

Device-Related Thrombus

Device-related thrombus remains a concern after LAAO. A study by Dukkipati et al[11] showed an incidence rate of 3.74%. Device-related thrombus increased the risk of stroke or systemic embolism 3 times. This study also identified factors that could predict device-related thrombus, including a history of TIA or cerebrovascular accident, permanent atrial fibrillation, vascular disease, LAA diameter, and left ventricular ejection fraction. It is essential to improve the risk assessment for device-related thrombus and develop devices with thromboresistant coatings, such as the WATCHMAN FLX Pro, to help reduce this risk.[12]

Amplatzer Amulet LAA Occluder vs WATCHMAN Device for Stroke Prophylaxis (Amulet IDE)

The AMPLATZER™ Amulet™ LAA Occluder Trial (Amulet IDE) trial (ClinicalTrials.gov identifier NCT02879448) enrolled 1878 patients across 108 sites (1598 patients at 78 US centers and 280 patients at 30 centers outside the United States). This study demonstrated the noninferiority of the Amulet occluder compared with the WATCHMAN device in terms of safety and efficacy for stroke prevention in patients with NVAF. The primary safety end point, a composite of procedure-related complications, all-cause death, or major bleeding at 12 months, occurred in 14.5% of patients who received the Amulet device and 14.7% of patients who received the WATCHMAN device. The primary effectiveness end point, a composite of ischemic stroke or systemic embolism at 18 months, was observed in 2.8% of patients in both groups.

The Amulet device did show superiority in achieving LAAO, with a success rate of 98.9% compared with 96.8% for the WATCHMAN device. It is important to note, however, that the Amulet device was associated with a higher rate of procedure-related complications, primarily driven by pericardial effusion and device embolization, particularly in the hands of less experienced implanters. The rates of major bleeding and other key secondary end points were similar between the 2 groups.

Compared with the first-generation WATCHMAN device, LAAO with a dual-seal mechanism using the Amulet occluder demonstrated noninferior safety and effectiveness, with superior LAAO rates but higher device-related complications. The increased risk of procedure-related complications, especially for less experienced operators, underscores the importance of careful patient selection and operator training. The choice between the 2 devices should be individualized based on patient factors and operator expertise. The clinical significance of differences in LAA closure will need to be ascertained through longer-term follow-up.[12]

Conclusion

The advancement of LAAO devices and techniques has made this procedure safer and more effective, providing a potential alternative to OAC therapy for stroke prevention among patients with NVAF. The WATCHMAN and Amplatzer Cardiac Plug devices have shown excellent stroke risk reduction with reassuring safety profiles. Continued research and development, such as the creation of devices with thromboresistant coating, may further improve the effectiveness of LAAO.

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