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WATCHMAN FLX™ Pro

12F

Left Atrial Appendage Closure Device with Delivery System

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℞ ONLY

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

REUSE WARNING

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess, or resterilize. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.

DEVICE DESCRIPTION

The WATCHMAN Left Atrial Appendage Closure (LAAC) Technology consists of an Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and Closure Device). The Access System and Delivery System permit Closure Device placement in the left atrial appendage (LAA) via femoral venous access and interatrial septum crossing into the left atrium.

The WATCHMAN FLX Pro Device is a self-expanding nitinol (nickel-titanium alloy) structure with a polyethylene terephthalate (PET) porous membrane on the proximal face. The Closure Device is coated with a hemo-compatible polyvinylidenefluoride-hexafluoropropylene (PVDF-HFP) coating. The Closure Device is constrained within the Delivery System until deployment in the LAA. The WATCHMAN FLX Pro Closure Device is compatible with all WATCHMAN Access Systems (Access Sheath and Dilator). The Closure Device is available in 6 sizes from 20 mm to 40 mm. Appropriate Closure Device sizing is determined by LAA measurements using fluoroscopy (fluoro), transesophageal echocardiographic, or intracardiac echocardiographic guidance.

Note: 3 RO (radiopaque) markers are aligned at the plane of maximum diameter of the Closure Device to aid in fluoroscopic assessment of the WATCHMAN FLX Pro Device.

Note: A clinical trial demonstrating safety and effectiveness of the WATCHMAN LAA Closure Technology (Access System and Delivery System) required the use of transesophageal echocardiography (TEE) during screening, implantation, and follow-up. There is clinical evidence to support the use of intracardiac echocardiography (ICE) and fluoroscopy to guide LAAC implantation (see details of ICE-LAA trial in Clinical Studies section).

The WATCHMAN FLX Pro Device is designed to be permanently implanted at the opening of the LAA to trap potential emboli before they exit the LAA. The placement procedure can be done under local or general anesthesia in a hospital cardiac catheterization or electrophysiology laboratory setting.

The WATCHMAN FLX Pro Device can be distinguished from the WATCHMAN FLX Device by the orange deployment knob.

Contents

Quantity	Description
1	WATCHMAN FLX Pro Left Atrial Appendage Closure Device with Delivery System

Materials

Table 1. Closure Device Materials

Material	Amount(s)*
Titanium Dioxide	0.0004 g
Polyethylene terephthalate (PET)	0.103 g
Nickel-titanium alloy (Nitinol)	0.380 g
Titanium grade 2	0.031 g
Polyvinylidene difluoride-hexafluoropropylene (PVDF- HFP)	0.0046 g
Tantalum	0.0010 g

*Materials are the same for all Closure Devices, but the amounts listed represent the 40 mm Closure Device, which contains the highest amount of each material.

Non-pyrogenic

This device meets pyrogen limit specifications.

User Information

Intended Users of the WATCHMAN FLX Pro Device are interventional cardiologists and/or electrophysiologists who are proficient in percutaneous procedures, transseptal procedures, the imaging modality utilized, and who have completed the WATCHMAN FLX Pro Physician Training program. Implantation of the WATCHMAN FLX Pro Device should only be performed by these Intended Users.

INTENDED USE

WATCHMAN FLX Pro is intended for percutaneous, transcatheter closure of the left atrial appendage.

INDICATIONS FOR USE

The WATCHMAN FLX Pro Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc[1] scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

CONTRAINDICATIONS

Do not use the WATCHMAN FLX Pro Device if:

- Intracardiac thrombus is present.
- An atrial septal defect repair or closure device is present.
- A patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a Closure Device (see **Step 7**).
- The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN FLX Pro Device is contraindicated.
- Any of the customary contraindications for other percutaneous catheterization procedure (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of anticoagulation therapy, aspirin, or $P2Y_{12}$ inhibitor.

WARNINGS

Implantation of the WATCHMAN FLX Pro Device should only be performed by interventional cardiologists and/or electrophysiologists who are proficient in percutaneous procedures, transseptal procedures, the imaging modality utilized and who have completed the WATCHMAN FLX Pro Physician Training program.

- For single use only. Do not reuse, reprocess, or resterilize. Reuse, reprocessing, or resterilization may compromise the structural integrity of the Closure Device and/or lead to Closure Device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the Closure Device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the Closure Device may lead to injury, illness, or death of the patient.
- This device has not been studied in pregnant or breastfeeding women. Careful consideration should be given to use of the Closure Device in pregnant and/ or breastfeeding women due to the risk of significant exposure to x-rays and the use of anticoagulation medication.
- Device selection should be based on accurate LAA measurements obtained using transesophageal or intracardiac echocardiographic imaging guidance in multiple views to avoid improper Closure Device sizing. For TEE recommended in multiple angles [e.g., 0°, 45°, 90°, 135°]; For ICE imaging, visualization of the LAA is recommended with the following anatomical structures: aortic valve (short-axis), mitral valve (long-axis), and pulmonary artery (short-axis), to assess the minimum and maximum diameter of the LAA ostium.
- Do not release (i.e., unscrew) the WATCHMAN FLX Pro Device from the core wire unless all release criteria (Step 15) are satisfied to avoid suboptimal results.
- Potential for Closure Device embolization exists with cardioversion < 30 days following Closure Device implantation; verify Closure Device position after cardioversion during this period.
- If thrombus is observed on the device, anticoagulation therapy is recommended until resolution of thrombus is demonstrated by TEE.
- Appropriate post-procedure drug therapy should be followed. See Post-Procedure Information section for further detail.
- Do not use if the temperature exposure indicator dot on the pouch label is red or missing, indicating Closure Device performance may have been compromised.

PRECAUTIONS

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN FLX Pro Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying, recapturing, and repositioning the Closure Device.
- Use caution when introducing a WATCHMAN Access System to prevent damage to cardiac structures.
- Use caution when introducing the Delivery System to prevent damage to cardiac structures.
- To prevent damage to the Delivery Catheter or Closure Device, do not allow the WATCHMAN FLX Pro Device to protrude beyond the distal tip of the Delivery Catheter when inserting the Delivery System into the Access Sheath.
- If using a power injector, the maximum pressure should not exceed 690 kPa (100 psi).
- Use caution when manipulating the Delivery System. Excessive counterclockwise rotation of the deployment knob or Delivery System hub independent from the rest of the Delivery System can cause premature implant detachment.

PATIENT SELECTION FOR TREATMENT

In considering the use of the WATCHMAN FLX Pro Device, the rationale for seeking an alternative to long-term anticoagulation therapy and the safety and effectiveness of the device compared to anticoagulation should be taken into account.

Non-valvular atrial fibrillation is associated with an increased risk of cardioembolic stroke. However, there are many sources of thromboembolism in patients with non-valvular atrial fibrillation. The WATCHMAN FLX Pro Device is designed to reduce the risk of thromboembolism originating from the LAA. Although thromboembolism from the LAA is a common source of stroke in this setting, it is not the sole source. Therefore, the WATCHMAN FLX Pro Device would not be expected to reduce the risk of ischemic stroke unrelated to cardioembolism from the LAA, and other potential risk factors for stroke should be considered (e.g., cerebrovascular disease, hypercoagulable states).

Approved oral anticoagulants effectively reduce the risk of cardioembolic stroke and are the most commonly used treatments in at-risk patients with non-valvular atrial fibrillation. Following a careful assessment of the safety and effectiveness of the available approved oral anticoagulants, the WATCHMAN FLX Pro Device is an option that may be considered in selected patients to reduce the risk of cardioembolism from the LAA.

Selection among available treatment options must first take into account whether anticoagulation is indicated to reduce the risk of stroke based on CHA_2DS_2-VASc scores. Next, in a patient who is deemed by their physicians to be suitable for anticoagulation therapy, physicians and patients should consider the rationale for implantation of the WATCHMAN FLX Pro Device as an alternative to long-term anticoagulation therapy. Specific factors may include one or more of the following:

- A history of major bleeding while taking anticoagulation therapy.
- The patient's prior experience with oral anticoagulation (if applicable).
- A medical condition, occupation, or lifestyle placing the patient at high risk of major bleeding secondary to trauma. Some studies of patients with a history of falls, or at risk for falls and head trauma, have shown that the benefits of anticoagulation therapy to reduce the risk of stroke outweigh the risk of major, life-threatening bleeding. An individualized benefit and risk assessment should be made in such patients.[2,3,4]
- The presence of indication(s) for long-term anticoagulation therapy, other than non-valvular atrial fibrillation (e.g. mechanical heart valve, hypercoagulable states, recurrent deep venous thrombosis).

Details regarding the indications, contraindications, warnings, and precautions for oral anticoagulants approved for patients with non-valvular atrial fibrillation are provided in their respective Instructions for Use. Of note:

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN FLX Pro Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.

Factors that need to be considered for the WATCHMAN FLX Pro Device and implantation procedure include the following:

- Overall medical status, including conditions which might preclude the safety of a percutaneous, transcatheter procedure.
- Suitability for percutaneous, transseptal procedures, including considerations of:
  - Cardiac anatomy relating to the LAA size and shape.
  - Vascular access anatomy (e.g., femoral vein size, thrombus, or tortuosity).
  - Ability of the patient to tolerate general or local anesthesia.
  - Ability of the patient to undergo required imaging.
- Ability to comply with the recommended post-WATCHMAN FLX Pro Device implant pharmacologic regimen (see Post Procedure Information section) especially for patients at high risk for bleeding.

[1] January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology 2019; 74(1): 104-132.

[2] American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons. J Am Geriat Soc. 2010 (http://www. americangeriatrics.org/files/documents/health_care_pros/JAGS.Falls.Guidelines.pdf)

[3] Seller MB, Newby LK. Atrial Fibrillation, Anticoagulation, Fall Risk, and Outcomes in Elderly Patients. Am Heart J. 2011; 161:241-246.

[4] Donzé J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy. Am J Med. 2012 Aug;125(8):773-8.

PATIENT COUNSELING INFORMATION

Physicians should review the following information when counseling patients about the WATCHMAN FLX Pro Device and implant procedure:

- The safety and effectiveness of systemic anticoagulation and localized percutaneous LAA closure with the Closure Device.

- There are non-LAA sources of cardiac emboli and other etiologies of stroke that may result in ischemic stroke independent of LAA closure that should be considered.
- The procedural risks associated with Closure Device implantation. **Tables 7** and **51** detail the major clinical events related to the device or procedure as observed in the WATCHMAN clinical trial program.
- The need for adherence to a defined pharmacologic regimen of anticoagulation therapy and antiplatelet therapy following WATCHMAN FLX Pro Device implantation.
- Clinical conditions may arise that require continuation or resumption of anticoagulation therapy following WATCHMAN FLX Pro Device implantation.
- The risk of the device implantation procedure plus post-procedure related bleeding weighed against the risk of bleeding on long-term anticoagulation therapy.
- MR Conditional (1.5 T and 3 T) immediately after implant.
- Any serious incident that occurs in relation to this device should be reported to Boston Scientific and the relevant local regulatory authority.

Additional counseling information can be found in the Patient Guide and in the clinical studies section of these Instructions for Use.

Implantable Device Patient Information

Advise the patient that additional information may be available to them on the Boston Scientific website (www.bostonscientific.com/ patientlabeling).

Implant Card Instructions

Record the institution name, patient details, and implant date. Add a peel-off label from product packaging. Provide the patient with the completed implant card and advise the patient to carry the card with them at all times. Instruct the patient to present the implant card to their Healthcare professionals (doctors, dentist, technicians) so they can take the necessary precautions.

MRI SAFETY INFORMATION

Table 2: MRI Safety Information

A person with the Boston Scientific WATCHMAN FLX Pro Closure Device may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.	
Device Name	WATCHMAN FLX Pro Closure Device
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
RF Receive Coil Type	Any
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back-to-back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact of up to 8 mm.

If information about a specific parameter is not included, there are no conditions associated with that parameter.

SUMMARY OF PRIMARY CLINICAL STUDIES

Treatment with the WATCHMAN Left Atrial Appendage Closure (LAAC) Device, a permanent implant intended to reduce the risk of thromboembolism from the LAA, was evaluated in subjects with non-valvular atrial fibrillation who are suitable for warfarin therapy. The pivotal WATCHMAN LAAC Therapy for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) study was followed by three additional studies in this population: a continued access (CAP) registry to the PROTECT AF study; and a second randomized study, the Prospective Randomized Evaluation of the WATCHMAN LAAC Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study; and a continued access (CAP2) registry to the PREVAIL study. Upon WATCHMAN LAAC Device approval, the New Enrollment PoST-approval Surveillance Analysis Plan (NESTed SAP) and the New Enrollment PoST Approval Surveillance Analysis Plan to Assess Safety for the Use of Dual AntiPlaTelet Post-Implant (NESTed-DAPT) prospectively enrolled patients that received a commercial device.

The Protection Against Embolism for Non-valvular AF Patients: Investigational Device Evaluation of the WATCHMAN FLX LAA Closure Technology (PINNACLE FLX) trial was a non-randomized study enrolling patients to receive the next generation WATCHMAN FLX Device. PINNACLE FLX evaluated subjects with non-valvular atrial fibrillation who were suitable for oral anticoagulation therapy and had a rationale to seek non-pharmacologic alternative. **Table 3** shows a summary of study designs, number of study subjects enrolled, and planned follow-up for each study. Transesophageal echocardiography (TEE) and fluoroscopy (fluoro) were used in the WATCHMAN pivotal clinical trials for selection of device size.

Table 3. Summary of WATCHMAN Clinical Studies

Patient Population	Subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for oral anticoagulation* (OAC) therapy to reduce the risk of ischemic stroke and systemic embolism							
Study	**PROTECT AF**	**CAP**	**PREVAIL**	**CAP2**	**NESTed SAP**	**NESTed-DAPT**	**PINNACLE FLX**	**ICE-LAA**
Purpose	Demonstrate safety and effectiveness of the WATCHMAN Device compared to long-term warfarin	Continued access registry	Demonstrate safety and effectiveness of the WATCHMAN Device compared to long-term warfarin	Continued access registry	Post approval surveillance analysis plan	Assess safety outcomes associated with DAPT instead of OAC and aspirin for immediate post-implant medication regimen	Demonstrate safety and effectiveness of the WATCHMAN FLX Device	Assess the use of ICE imaging of the LAA during WATCHMAN FLX LAAC implant procedure
Device	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN FLX	WATCHMAN FLX
Study Design	2:1 Randomized, non-inferiority	Non-randomized	2:1 Randomized, non-inferiority	Non-randomized	Non-randomized	Non-randomized registry surveillance analysis	Non-randomized	Non-randomized
Primary Endpoints	1. Effectiveness: Stroke, cardiovascular death, and systemic embolism 2. Safety: Life-threatening events which include device embolization requiring retrieval and bleeding events		1. Effectiveness: Stroke, systemic embolism, and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after seven days post-randomization or WATCHMAN implant procedure 3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications** within seven-days of the implantation procedure		1. Effectiveness: Stroke, systemic embolism, and all-cause death 2. Effectiveness: Ischemic stroke or systemic embolism 3. Safety: Death, ischemic stroke, systemic embolism and procedure/ device-related complications** within seven-days of the implantation procedure	1. Composite: all-cause death, stroke, major bleed, and systemic embolism between date of hospital discharge and 45-days post-procedure. 2. Ischemic Stroke Performance Goal: The 97.5% one-sided upper confidence limit of the observed Ischemic Stoke event rate between the date of hospital discharge and 45-days post-procedure for the DAPT Cohort must be ≤ 1.4%.	1. Effectiveness: The rate of effective LAA closure defined as any peri-device leak ≤ 5mm demonstrated by TEE at 12 months. 2. Safety: Death, ischemic stroke, systemic embolism and procedure/ device-related complications** within seven-days of the implantation procedure	1. Effective closure of the LAA, defined as no significant leak (>5 mm), based on the 45-day post-implant TEE and assessed by the echocardiography core laboratory.
Number of Patients Enrolled	800 subjects • 93 roll-in WATCHMAN • 707 randomized o 463 WATCHMAN o 244 Control	566 WATCHMAN subjects	461 subjects • 54 roll-in WATCHMAN • 407 randomized o 269 WATCHMAN o 138 Control	576 WATCHMAN subjects	Primary Cohort: 1000 subjects Secondary Cohort: 1000 subjects	Propensity Matched Primary Cohort: • 1036 DAPT • 1036 Control	458 subjects • 58 roll-in • 400 WATCHMAN FLX	100 subjects
Status of Subject Follow-Up	Study Complete 2717 patient-years	Study Complete 2293 patient-years	Study Complete 1626 patient-years	Study Complete 2329 patient-years	Study Ongoing 839 patient-years	Study Complete	Study Complete	Study Complete

Patient Population	Subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for oral anticoagulation* (OAC) therapy to reduce the risk of ischemic stroke and systemic embolism							
Study	**PROTECT AF**	**CAP**	**PREVAIL**	**CAP2**	**NESTed SAP**	**NESTed-DAPT**	**PINNACLE FLX**	**ICE-LAA**
Post Implant Drug Regiment	45-days warfarin + aspirin then DAPT (Dual Antiplatelet Therapy) until 6-months	45-days warfarin + aspirin then DAPT until 6-months	45-days warfarin + aspirin then DAPT until 6-months	45-days warfarin + aspirin then DAPT until 6-months	45-days warfarin + aspirin then DAPT until 6-months	DAPT: 45-days $P2Y_{12}$ + aspirin Control: 45-days warfarin + aspirin	45-days NOAC (Non-Vitamin K antagonist oral anticoagulant) + aspirin then DAPT until 6-months	Standard of care
Scheduled Follow-Up Duration	5 years					45-days	2 years	45-days

* PROTECT AF, CAP, PREVAIL, CAP2, and NESTed-SAP studies recommended warfarin, and PINNACLE FLX recommended non-vitamin K antagonist OAC (NOAC). NESTed-DAPT assessed warfarin subjects in Control cohort.

** Events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair complications within seven-days of the implantation procedure.

PROTECT AF Study

The PROTECT AF study was a multicenter, prospective randomized controlled study comparing the WATCHMAN Device to long-term warfarin therapy. The purpose of the study was to demonstrate that the WATCHMAN Device is safe and effective in subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for warfarin therapy. A 2:1 randomization allocation ratio was used with stratification by center such that for every one subject randomized to the Control arm (long-term warfarin therapy); two subjects were randomized to the Device arm to receive the WATCHMAN Device.

The primary effectiveness composite endpoint was the rate of the composite of stroke (including ischemic and hemorrhagic), systemic embolism, and cardiovascular death (cardiovascular and unexplained). The primary safety endpoint was the rate of life-threatening events as determined by the Clinical Events Committee (CEC), which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitated a surgical procedure. The primary statistical objective was to determine if the device group is non-inferior to the Control group with respect to the event rate for the composite primary effectiveness endpoint.

A total of 800 subjects were enrolled in the study at 59 centers. The 800 subjects included 463 subjects randomized to the WATCHMAN Device group, 244 subjects randomized to the Control group, and 93 roll-in WATCHMAN Device subjects.

PREVAIL Study

The PREVAIL study was a multicenter, prospective randomized controlled study to evaluate the safety and effectiveness of the WATCHMAN Device compared to long-term warfarin therapy. PREVAIL was a second pivotal, randomized study of the WATCHMAN Device, and the analyses of the primary endpoints included historical data from the PROTECT AF study.

There were three primary endpoints (two effectiveness and one safety) as follows: 1) the composite of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular or unexplained death; 2) the composite ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following randomization; and 3) the occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever is later. A total of 461 subjects at 41 U.S. investigational sites were enrolled from November 2010 through June 2012. The 461 subjects included 269 subjects randomized to the WATCHMAN Device group, 138 subjects randomized to the Control group, and 54 roll-in WATCHMAN Device subjects.

CAP Registry

The CAP registry was a multi-center prospective non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Entry criteria were the same as the PROTECT AF study. A total of 26 centers (24 U.S., 2 European) actively participated by enrolling at least one subject in the study. A total of 566 subjects were enrolled from August 2008 through June 2010.

The primary effectiveness and safety endpoints were similar to the PROTECT AF.

CAP2 Registry

The CAP2 registry is a multi-center prospective non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Entry criteria were the same as the PREVAIL study. A total of 576 subjects at 47 U.S. investigational sites were enrolled from September 2012 through March 2014.

The primary effectiveness and safety endpoints were similar to the PREVAIL study.

NESTed Surveillance Analysis Plan

The NESTed registry assesses long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN Device in a routine clinical setting.

The WATCHMAN New Enrollment PoST Approval Surveillance Analysis Plan (NESTed SAP) is a multi-center, prospective, non-randomized registry utilizing data captured in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR). Two cohorts of 1,000 patients (primary and secondary) will be included in the analysis. The Primary Cohort will consist of subjects who are eligible for a WATCHMAN Device according to current U.S. indications with a calculated $CHADS_2$ score of ≥ 2 or a CHA_2DS_2-VASc score of ≥ 3 and exclude any patients who are contraindicated for a WATCHMAN Device according to this document or patients with concomitant cardiac or non-cardiac procedures (including, but not limited to: cardiac ablation, trans-catheter valve implantation, coronary intervention, etc.). Once the primary cohort was complete, the next consecutive 1,000 patients implanted were included in the secondary cohort.

NESTed-DAPT Surveillance Analysis

The NESTed-DAPT registry study assessed safety outcomes associated with the use of dual antiplatelet therapy (DAPT) instead of OAC and aspirin as the immediate post-implant medication regimen for the WATCHMAN Left Atrial Appendage (LAA) Closure Technology in a routine clinical setting.

The WATCHMAN New Enrollment PoST Approval Surveillance Analysis Plan to Assess Safety for the Use of Dual AntiPlaTelet Post-Implant (NESTed-DAPT) was an observational, prospective, non-randomized, multicenter registry surveillance analysis utilizing data captured in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR). Two propensity-matched cohorts of 2072 patients (1036 DAPT and 1036 Control) were included in the primary analysis. The Primary Cohort included subjects enrolled in the LAAO Registry who successfully received a WATCHMAN implant with a calculated CHA_2DS_2-VASc score of ≥ 2 in men and ≥ 3 in women and excluded patients with concomitant cardiac or non-cardiac procedures (including, but not limited to: cardiac ablation, trans-catheter valve implantation, coronary intervention).

PINNACLE FLX Study

PINNACLE FLX is a prospective, non-randomized, multi-center investigation to establish the safety and effectiveness of the WATCHMAN FLX LAA Closure Device for subjects with non-valvular atrial fibrillation who are eligible for long-term non-vitamin K antagonist oral anticoagulation (NOAC) therapy to reduce the risk of stroke but who have a rationale to seek a non-pharmacologic alternative.

This study had two primary endpoints: 1) The rate of effective LAA closure defined as any peri-device leak ≤ 5 mm demonstrated by TEE at 12 months; and 2) the occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention between the time of implant and 7 days following the procedure or by hospital discharge, whichever was later.

ICE-LAA Study

The ICE-LAA is a prospective, non-randomized, single-arm, multi-center investigation to assess the use of ICE imaging of the LAA during the WATCHMAN FLX LAAC implant procedure. A total of 100 subjects at 7 European sites were enrolled from July 2020 to September 2021. The primary endpoint was effective closure of the LAA, defined as no significant leak (>5 mm), based on the 45-day post-implant TEE and assessed by the echocardiography core laboratory.

Table 4. Summary of Baseline Demographics (WATCHMAN 2.5)

	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP N=1000	NESTed-DAPT (WATCHMAN 2.5)		
Characteristic	**WATCHMAN N=463**	**Control N=244**	**P-value**	**WATCHMAN N=269**	**Control N=138**	**P-value**				**DAPT N = 1036**	**Control N = 1036**	**P-value**
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	72.7 ± 9.2 (244) (41.0, 95.0)	0.179	74.0 ± 7.4 (269) (50.0, 94.0)	74.9 ± 7.2 (138) (53.0, 90.0)	0.260	74.0 ± 8.3 (566) (44.0, 94.0)	75.3 ± 8.0 (576) (33.0, 94.0)	76.5 ± 8.1 (37.0, 100.0)	77.0±7.6 (1036) (49.0, 95.0)	77.1±7.0 (1036) (52.0, 94.0)	0.876
Sex												
Female	137/463 (29.6%)	29.9% (73/244)	0.928	32.3% (87/269)	25.4% (35/138)	0.146	34.5% (195/566)	39.4% (227/576)	38.1% (381/1000)	43.7% (453/1036)	44.1% (457/1036)	0.860
Male	326/463 (70.4%)	70.1% (171/244)		67.7% (182/269)	74.6% (103/138)		65.5% (371/566)	60.6% (349/576)	61.9% (619/1000)	56.3% (583/1036)	55.9% (579/1036)	
Race/Ethnicity												
American Indian or Alaskan	N/A	N/A	0.779	N/A	N/A	0.603	N/A	0.3% (2/576)	0.4% (4/1000)	0.0% (0/1036)	0.1% (1/1036)	1.000
Asian	0.9% (4/463)	0.4% (1/244)		0.4% (1/269)	0.7% (1/138)		1.6% (9/566)	0.7% (4/576)	1.3% (13/1000)	1.5% (16/1036)	1.6% (17/1036)	0.861
Black/African American	1.3% (6/463)	2.0% (5/244)		2.2% (6/269)	0.7% (1/138)		1.9% (11/566)	1.2% (7/576)	4.0% (40/1000)	7.7% (80/1036)	6.6% (68/1036)	0.306
Caucasian	91.8% (425/463)	91.0% (222/244)		94.1% (253/269)	94.9% (131/138)		91.9% (520/566)	94.1% (542/576)	93.9% (939/1000)	90.1% (933/1036)	91.1% (944/1036)	0.408
Hispanic/ Latino	5.4% (25/463)	6.1% (15/244)		2.2% (6/269)	3.6% (5/138)		3.5% (20/566)	2.1% (12/576)	4.0% (40/1000)	3.4% (35/1029)	2.2% (23/1029)	0.110
Hawaiian/ Pacific Islander	(0.2%) (1/463))	0.4% (1/244)		0.4% (1/269)	0.0% (0/138)		0.2% (1/566)	0.0% (0/576)	N/A	0.1% (1/1036)	0.0% (0/1036)	1.000
Other	2/463 (0.4%)	0.0% (0/244)		0.7% (2/269)	0.0% (0/138)		0.9% (5/566)	0.7% (4/576)	0.7% (7/1000)	0.6% (6/1036)	0.6% (6/1036)	1.000
AF Pattern												
Paroxysmal AF	43.2% (200/463)	40.6% (99/244)	0.762	48.7% (131/269)	51.4% (71/138)	0.571	42.8% (242/566)	53.6% (309/576)	44.8% (448/1000)	59.7% (618/1036)	59.7% (618/1036)	1.000
Persistent AF	21.0% (97/463)	20.5% (50/244)		31.6% (85/269)	28.3% (39/138)		30.2% (171/566)	25.7% (148/576)	36.0% (360/1000)	25.9% (268/1036)	25.0% (259/1036)	0.650
Permanent AF	34.6% (160/463)	38.1% (93/244)		15.6% (42/269)	15.9% (22/138)		24.0% (136/566)	14.4% (83/576)	18.7% (187/1000)	14.5% (150/1036)	15.3% (159/1036)	0.579
Paced AF	N/A	N/A		2.6% (7/269)	3.6% (5/138)		0% (0/566)	6.3% (36/576)	N/A	N/A	N/A	N/A
Unknown	1.3% (6/463)	0.8% (2/244)		1.5% (4/269)	0.7% (1/138)		3.0% (17/566)	0% (0/576)	0.2% (2/1000)	0.2% (2/1036)	0.5% (5/1036)	0.452

Table 5. Summary of Baseline Demographics (WATCHMAN FLX)

Demographic	NESTed-DAPT (WATCHMAN FLX)			PINNACLE FLX N=400	ICE-LAA N=100
	DAPT N = 1461	**Control N = 1741**	**P-value**		
Age, years	77.1±7.6 (1461) (47.0-100.0)	76.5±7.6 (1741) (26.0-100.0)	0.0271	73.8 ± 8.6 (400) (44.0, 98.0)	75.8±7.7 (100) (48.0, 94.0)
Sex					
Female	40.8% (596/1461)	39.1% (680/1741)	0.3176	35.5% (142/400)	33% (33/100)
Male	59.2% (865/1461)	60.9% (1061/1741)		64.5% (258/400)	67% (67/100)
Race/Ethnicity					
American Indian or Alaskan	0.2% (3/1461)	0.4% (7/1741)	0.3617	0.3% (1/382)	N/A
Asian	1.5% (22/1461)	1.0% (17/1741)	0.1738	0.5% (2/382)	N/A
Black/African American	5.7% (83/1461)	2.8% (48/1741)	< 0.0001	4.7% (18/382)	N/A
Caucasian	91.6% (1339/1461)	94.9% (1653/1741)	0.0002	93.7% (358/382)	N/A
Hispanic/Latino	2.2% (32/1443)	2.6% (45/1732)	0.4876	2.6% (10/382)	N/A
Hawaiian/ Pacific Islander	0.0% (0/1461)	0.1% (2/1741)	0.5037	0.0% (0/382)	N/A
Other	2.7% (39/1461)	2.4% (41/1741)	0.5702	0.0% (0/382)	N/A
AF Pattern					
Paroxysmal AF	64.1% (932/1455)	57.7% (1004/1740)	0.0003	51.8% (207/400)	44.0% (44/100)
Persistent AF	23.3% (339/1455)	24.1% (420/1740)	0.5790	36.5% (146/400)	15.0% (15/100)
Permanent AF	12.6% (184/1455)	18.2% (316/1740)	< .0001	10.5% (42/400)	41.0% (41/100)
Paced AF	N/A	N/A	N/A	1.3% (5/400)	N/A
Unknown	0.4% (6/1461)	0.1% (1/1741)	0.0523	N/A	0.0% (0/100)

Table 6. Summary of Baseline Characteristics (WATCHMAN 2.5)

Characteristic	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP N=1000	NESTed-DAPT (WATCHMAN 2.5)		
	WATCHMAN N=463	Control N=244	P-value	WATCHMAN N=269	Control N=138	P-value				DAPT N = 1036	Control N = 1036	P-value
$CHADS_2$ Score (Continuous)	2.2±1.2 (463) (1.0, 6.0)	2.3±1.2 (244) (1.0, 6.0)	0.072	2.6 ± 1.0 (269) (1.0, 6.0)	2.6 ± 1.0 (138) (1.0 ,5.0)	0.838	2.5 ± 1.2 (566) (1.0, 6.0)	2.7±1.1 (576) (1.0, 6.0)	3.2 ±1.2 (1000) (0.0, 6.0)	3.1 ±1.3 (1036) (0.0, 6.0)	3.0 ±1.2 (1036) (0.0, 6.0)	0.606
CHA_2DS_2-VASc Score (Continuous)	3.2±1.4 (460)	3.5±1.5 (239)	0.022	4.0 ± 1.1 (269) (2.0, 8.0)	4.1 ± 1.2 (138) (2.0, 7.0)	0.399	3.9 ± 1.5 (564) (1.0, 9.0)	4.5±1.3 (576) (2.0, 9.0)	5.0±1.4 (1000) (2.0, 9.0)	5.1±1.5 (1036) (2.0-9.0)	5.0±1.3 (1036) (2.0-9.0)	0.674
CHF	26.8% (124/463)	27.0% (66/244)	0.9392	23.4% (63/269)	23.2% (32/138)	0.958	19.1% (108/566)	27.1% (156/576)	N/A	40.9% (424/1036)	38.9% (403/1036)	0.346
Hypertension	89.6% (415/463)	90.2% (220/244)	0.8243	88.5% (238/269)	97.1% (134/138)	0.003	89.0% (503/565)	92.5% (533/576)	N/A	92.6% (959/1036)	93.1% (965/1036)	0.609
Age 65-74	N/A	N/A	N/A	N/A	N/A	N/A	37.5% (212/566)	N/A	N/A	30.5% (316/1036)	29.3% (304/1036)	0.565
Age > =75	41.0% (190/463)	47.1% (115/244)	0.1198	52.0% (140/269)	56.5% (78/138)	0.391	51.8% (293/566)	59.5% (344/576)	N/A	64.6% (669/1036)	66.3% (687/1036)	0.406
Diabetes	24.4% (113/463)	29.5% (72/244)	0.1423	33.8% (91/269)	29.7% (41/138)	0.401	24.9% (141/566)	33.7% (194/576)	N/A	39.5% (409/1036)	39.7% (411/1036)	0.928
Previous stroke, TIA, or TE	17.7% (82/463)	20.1% (49/244)	0.4404	27.5% (74/269)	28.3% (39/138)	0.873	30.4% (172/566)	29.0% (167/576)	N/A	33.9% (351/1036)	32.2% (334/1036)	0.427
Vascular disease	N/A	N/A	N/A	N/A	N/A	N/A	45.1% (255/566)	45.8% (265/576)	N/A	58.2% (603/1036)	58.7% (608/1036)	0.824
HAS-BLED Score (Continuous)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.00 ± 0.94 (576) (0.00, 5.00)	2.7±1.1 (1000) (0.0, 6.0)	2.7±1.0 (1036) (0.0, 7.0)	2.7±1.0 (1036) (0.0, 6.0)	0.173

Table 7. Summary of Baseline Characteristics (WATCHMAN FLX)

Characteristic	NESTed-DAPT (WATCHMAN FLX)			PINNACLE FLX N=400	ICE-LAA N=100
	DAPT N = 1461	Control N = 1741	P-value		
$CHADS_2$ Score (Continuous)	N/A	N/A	N/A	2.3 ± 1.2 (400) (0, 6.0)	N/A
CHA_2DS_2-VASc Score (Continuous)	5.1±1.5 (1461) (2.0-9.0)	4.9±1.5 (1741) (2.0-9.0)	< .0001	4.2+1.5 (400) (2.0, 9.0)	4.0±1.5 (100) (1.0, 8.0)
CHF	41.8% (611/1461)	41.3% (719/1741)	0.7650	31.8% (127/400)	13.0% (13/100)
Hypertension	92.4% (1350/1461)	92.9% (1617/1741)	0.6075	85.8% (343/400)	79.0% (79/100)
Age 65-74	28.4% (415/1461)	31.8% (553/1741)	0.0393	35.8% (143/400)	31.0% (31/100)
Age > =75	66.2% (967/1461)	63.1% (1098/1741)	0.0661	50.5% (202/400)	60.0% (60/100)
Diabetes	39.9% (583/1461)	38.3% (667/1741)	0.3574	30.5% (122/400)	27.0% (27/100)
Previous stroke, TIA, or TE	36.6% (535/1461)	32.8 (571/1741)	0.0235	22.3% (89/400)	26.0% (26/100)
Vascular disease	60.2% (880/1461)	54.5% (949/1741)	0.0011	55.0% (220/400)	35.0% (35/100)
HAS-BLED Score (Continuous)	2.6±1.0 (1457) (0.0-8.0)	2.6±1.1 (1737) (0.0-6.0)	0.0182	2.0±1.0 (400) (0.0, 5.0)	2.5±0.9 (100) (0.0, 5.0)

Observed adverse events related to the WATCHMAN Device or implantation procedure (as evaluated by the Clinical Events Committee) in patients from the PROTECT AF, CAP, PREVAIL and CAP2 studies are shown in **Table 8.**

Table 8. PROTECT AF, CAP, PREVAIL, and CAP2 Major Clinical Events Related to the WATCHMAN Device or Implant**

Event	PROTECT AF n (%) N=463	CAP n (%) N=566	PREVAIL n (%) N=269	CAP2 n (%) N=576
Pericardial effusion with cardiac tamponade	13 (2.8)	7 (1.2)	4 (1.5)	8 (1.4)
Pseudoaneurysm	3 (0.6)	5 (0.9)	0 (0.0)	3 (0.5)
Device embolization	3 (0.6)	1 (0.2)	2 (0.7)	0 (0.0)
Ischemic stroke related to device or implant procedure*	7 (1.5)	2 (0.4)	4 (1.5)	12 (2.0)
Ischemic stroke related to device thrombus	2 (0.4)	2 (0.4)	3 (1.1)	4 (0.7)
Ischemic stroke related to air embolism	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic stroke related to procedure (excluding air embolism and device thrombus)	2 (0.4)	0 (0.0)	1 (0.4)	8 (1.4)
Systemic embolism*	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.3)
Pericardial effusion - no intervention required	4 (0.9)	5 (0.9)	0 (0.0)	3 (0.5)
Cardiac perforation (surgical repair)	7 (1.5)	1 (0.2)	1 (0.4)	3 (0.5)
Bruising or hematoma	4 (0.9)	1 (0.2)	2 (0.7)	2 (0.3)
Major bleed requiring transfusion	1 (0.2)	5 (0.9)	3 (1.1)	3 (0.5)
Groin bleeding	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	4 (0.7)	2 (0.7)	4 (0.7)
Infection	2 (0.4)	0 (0.0)	3 (1.1)	1 (0.2)
Arrhythmias	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
Transient ischemic attack (TIA)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)
AV fistula	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
Chest pain	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Atrial septal defect	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Ventricular tachycardia	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Device migration	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

*The overall rates of ischemic stroke and systemic embolism, including those independent of the WATCHMAN Device implant procedure, are shown in **Table 10**, **Table 18**, **Table 26**, and **Table 31**.

** Please note, due to differences in the methodologies for event adjudication and for assessment of device/procedure relatedness among the studies, the results of PINNACLE FLX (**Table 52**) are not directly comparable to the results of the studies in **Table 8**.

ADVERSE EVENTS

Potential adverse events which may be associated with the use of a left atrial appendage closure device or implantation procedure include but are not limited to:

- Air embolism
- Airway trauma
- Allergic reaction to the contrast media, anesthetic, WATCHMAN Implant material, or medication
- Altered mental status
- Anemia requiring transfusion
- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- Bruising, hematoma, or seroma near the catheter insertion site
- Cardiac perforation
- Chest pain/discomfort
- Confusion post-procedure
- Congestive heart failure
- Contrast-related nephropathy
- Cranial bleed
- Death
- Decreased hemoglobin
- Deep vein thrombosis
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Embolism
- Excessive bleeding
- Fever
- Fistula
- Groin pain
- Groin puncture bleed
- Hematuria
- Hemoptysis
- Hypotension
- Hypoxia
- Improper wound healing
- Inability to reposition, recapture, or retrieve the device
- Infection/pneumonia
- Interatrial septum thrombus
- Intratracheal bleeding
- Major bleeding requiring transfusion
- Misplacement of the device/improper seal of the appendage/movement of device from appendage wall
- Myocardial erosion
- Myocardial infarction
- Nausea
- Oral bleeding
- Pericardial effusion/tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Radiation injury
- Renal failure
- Respiratory insufficiency/failure
- Stroke - Hemorrhagic
- Stroke - Ischemic
- Surgical removal of the device
- TEE complications (e.g., throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular or vascular damage
- Vasovagal reactions

There may be other potential adverse events that are unforeseen at this time.

CLINICAL STUDIES

PROTECT AF Study

Primary Objective: To demonstrate that the WATCHMAN Device is safe and effective in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy to prevent thromboembolism from the LAA.

Design: The PROTECT AF study was a multi-center prospective randomized controlled trial comparing the WATCHMAN Device to long-term warfarin therapy. A 2:1 randomization allocation ratio (two Device subjects to one Control subject) was used with stratification by center.

Main entry criteria included, but were not limited to, at least 18 years of age, non-valvular atrial fibrillation, a $CHADS_2$ score of 1 or greater, and eligibility for long-term warfarin therapy. Following randomization, subjects were assessed at 45 days, at 6-, 9-, and 12-month visits, and semi-annually thereafter through 5 years. A non-randomized roll-in phase was added to permit physicians to become experienced with the WATCHMAN Device implant procedure. Subjects randomized to receive the WATCHMAN Device underwent TEE at 45 days, 6-, and 12-month visits after successful implantation. Subjects randomized to the Control group were to remain on warfarin with INR monitored every other week through 6 months and monthly thereafter.

The primary effectiveness endpoint was the rate of the composite of stroke (including ischemic and hemorrhagic), systemic embolism, cardiovascular death (cardiovascular and unexplained). The primary safety endpoint was rate of life-threatening events, which included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

The effectiveness event rate was defined as the number of events per 100 pt-yrs of follow-up. A Bayesian Poisson-Gamma model stratified by $CHADS_2$ score was used for evaluation of the statistical objective. The first sequential interim analysis was performed after collection of 600 pt-yrs of follow-up, which included 300 subjects with one year of follow-up and 100 subjects with two years of follow-up. Subsequent analyses were allowed after each additional 150 pt-yrs up to a maximum of 1500 pt-yrs of follow-up. The criterion for establishing non-inferiority at an interim analysis required that the posterior probability that the primary effectiveness event rate for the WATCHMAN group being less than 2 times the event rate for the Control group be at least 0.975 (or equivalently, the upper bound of the equitailed 2-sided 95% credible interval for the rate ratio be less than 2).

Enrollment: The study enrolled 800 subjects with 707 randomized and the remaining 93 participating in the WATCHMAN roll-in group. Of the 707 randomized subjects, 463 were assigned to the WATCHMAN group and 244 assigned to the warfarin control group as shown in **Table 9**.

Table 9. PROTECT AF Enrollment

Group	N
WATCHMAN Device Group	
Randomized	463
Implant Attempted	449
Device Implanted	408
Control Group	
Randomized	244
Warfarin Administered	241
Warfarin Never Administered	3
Roll-in Group	
Enrolled	93
Implant Attempted	93
Device Implanted	77

The PROTECT AF study is complete with 5 years and 2717 patient years of follow-up.

Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.2 ± 1.2, the mean CHA_2DS_2-VASc score was 3.2 ± 1.4, the mean age was 72 years, 70% were male, and 92% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.3 ± 1.2, the mean CHA_2DS_2-VASc score was 3.5 ± 1.6, the mean age was 73 years, 70% were male, and 91% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Tables 4** and **6**.

Results: WATCHMAN Device implant success (defined as successful release of the device) was achieved in 408/449 (90.9%) subjects who underwent the implant procedure.

Effectiveness: Results of the final 5 year follow-up representing 2717 patient years for the primary effectiveness endpoint of the composite of stroke, systemic embolism, and death (cardiovascular or unexplained) are displayed in **Table 10**. The primary effectiveness event rate was 2.2 events per 100 patient years for the Device group and 3.7 events per 100 patient years for the Control group, resulting in a relative risk or rate ratio of 0.61. The criterion for non-inferiority and superiority of the WATCHMAN Device vs. the Control group were met and were driven by the rates of hemorrhagic stroke and cardiovascular or unexplained death in favor of the Device group. The ischemic stroke rate numerically favored the control group.

Table 10. PROTECT AF Primary Effectiveness Results (Intent-to-Treat) and % of subjects who experienced 1 or more events (2717 patient years)

Randomization Allocation (2 Device: 1 Control)

	WATCHMAN		Control		
	Event Rate (per 100 Pt-yrs)	Event Rate/ Subject	Event Rate (per 100 Pt-yrs)	Event Rate/ Subject	Rate Ratio (95% CrI)*
Primary effectiveness	2.2 (40/1788)	8.6% (40/463)	3.7 (34/929)	13.9% (34/244)	0.61 (0.42, 1.07)
Ischemic stroke	1.3 (24/1782)	5.2% (24/463)	1.1 (10/933)	4.1% (10/244)	
Hemorrhagic stroke	0.2 (3/1838)	0.6% 3/463)	1.1 (10/946)	4.1% (10/244)	
Systemic embolism	0.2 (3/1837)	0.6% (3/463)	0.0 (0/949)	0.0% (0/244)	
Death (CV/ unexplained)	1.0 19/1843)	4.1% (19/463)	2.3 (22/949)	9.0% (22/244)	
Ischemic stroke and systemic embolism	1.5 (26/1781)	5.6% (26/463)	1.1 (10/933)	4.1% (10/244)	
Stroke (all)	1.5 (26/1782)	5.6% (26/463)	2.2 (20/929)	8.2% (20/244)	

*Posterior probability > 0.999 for non-inferiority and 0.954 for superiority

The Rate Ratio is based on the event rates per 100 pt-yrs

CrI = credible interval

Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)

Rel.risk = relative risk or rate ratio, calculated as Device rate over Control rate.

The primary effectiveness endpoint for PROTECT AF is shown as time to event in a Kaplan-Meier curve in **Figure 1.**

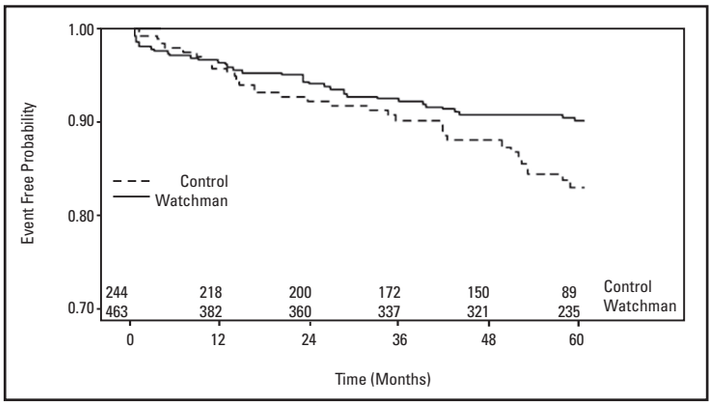


Figure 1. PROTECT AF Primary Effectiveness (2717 patient-years)

Safety: The primary safety rate was 3.5 events per 100 patient years for the Device group and 3.2 events per 100 patient years for the Control group resulting in a relative risk ratio of 1.08. These results are summarized in **Table 11**.

Table 11. PROTECT AF Primary Safety Results (Intent-to-Treat) (2717 patient-years)

Randomization Allocation (2 Device: 1 Control)

WATCHMAN Rate (N events/total pt-yrs)	Control Rate (N events/total pt-yrs)	Relative Risk (95% CrI)
3.5 (60/1729.6)	3.2 (29/904.9)	1.08 (0.72, 1.77)

*Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)*

Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

CrI = credible interval

PROTECT AF Major Bleeding Analysis

The rates of major bleeding complications, defined as bleeding events adjudicated as serious adverse events, are shown in **Table 12**. There were more bleeding events in the WATCHMAN group immediately post-procedure through day 45 with a lower rate of bleeding thereafter. The overall major bleeding rates were similar between the WATCHMAN group and the Control group.

Table 12. PROTECT AF Major Bleeding

	WATCHMAN		Control	
Major Bleeding	N Events/ Subjects (%)	Rate per 100 Pt-yrs (N Events/Total Pt-yrs)	N Events/ Subjects (%)	Rate per 100 Pt-yrs (N Events/Total Pt-yrs)
Procedure-related	28/463 (6.0%)	NA	NA	NA
Non-procedure related	24/463 (5.2%)	1.3 (24/1803.7)	29/244 (11.9%)	3.2 (29/904.9)
0-45 days	5/463 (1.1%)	9.2 (5/54.6)	2/244 (0.8%)	6.7 (2/29.7)
46 days – 6 months	4/431 (0.9%)	2.6 (4/153.6)	4/239 (1.7%)	4.6 (4/87.8)
> 6 months	15/397 (3.8%)	0.9 (15/1595.5)	23/228 (10.1%)	2.9 (23/787.5)
Total major bleeding	50/463 (10.8%)	2.9 (50/1743.4)	29/244 (11.9%)	3.2 (29/904.9)

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN and Control groups is presented in **Table 13**. Serious adverse events related to the WATCHMAN Device or implant procedure are shown in **Table 8**.

Table 13. PROTECT AF Serious Adverse Events

Event	WATCHMAN N=463			Control N=244		
	Number of Events	Number of Subjects	Percent of Subjects	Number of Events	Number of Subjects	Percent of Subjects
Adjudicated as Non-Event	1	1	0.2%	0	0	0
Anemia Requiring Transfusion	2	2	0.4%	1	1	0.4%
Arrhythmias	2	2	0.4%	0	0	0
AV Fistula	1	1	0.2%	0	0	0
Bleeding from Varicose Veins	1	1	0.2%	0	0	0
Bruising - Hematoma	5	5	1.1%	0	0	0
Cardiac Perforation	7	7	1.5%	0	0	0
Cranial Bleed	4	4	0.9%	1	1	0.4%
Death	59	59	12.7%	44	44	18.0%
Device Embolization	4	3	0.6%	0	0	0
Device Thrombus	2	2	0.4%	0	0	0
Epistaxis	4	4	0.9%	0	0	0
Gastrointestinal Bleeding	32	26	5.6%	27	22	9.0%
Hematuria	4	4	0.9%	0	0	0
Infection	2	2	0.4%	0	0	0
Major Bleed Requiring Transfusion	2	2	0.4%	1	1	0.4%
Oral Bleeding	0	0	0	1	1	0.4%
Other Study Related	18	17	3.7%	2	2	0.8%
Pericardial Effusion with Cardiac Tamponade	13	13	2.8%	0	0	0
Pericardial Effusion-Serious	4	4	0.9%	0	0	0
Pleural Effusion	1	1	0.2%	0	0	0
Pseudoaneurysm	3	3	0.6%	0	0	0
Pulmonary Edema	1	1	0.2%	0	0	0
Rectal Bleeding	1	1	0.2%	1	1	0.4%
Stroke - Hemorrhagic	3	3	0.6%	10	10	4.1%
Stroke - Ischemic	26	24	5.2%	11	10	4.1%
Systemic Embolization	3	3	0.6%	0	0	0
Thrombosis	1	1	0.2%	0	0	0
Transient Ischemic Attack	5	5	1.1%	0	0	0

PROTECT AF Device Thrombus Rates

The device thrombus-related stroke rate was 0.1 events per 100 patient-years as shown in **Table 14**.

Table 14. PROTECT AF Device-related Thrombus

	N=408
Thrombus Subjects	16 (3.9%)
Thrombus Events	17
Experienced Ischemic Stroke	2
Experienced Serious Adverse Event	3
Device Thrombus-Related Stroke Rate (per 100 pt-yrs)	0.1

Discontinuation of warfarin among WATCHMAN subjects: Among subjects successfully implanted with the WATCHMAN Device, 87% discontinued warfarin therapy by 45 days, and 93% discontinued warfarin therapy by 12 months.

PREVAIL Study

Primary Objective: To evaluate the safety and effectiveness of the WATCHMAN Device in subjects with atrial fibrillation who are deemed by their physicians to be suitable for long term warfarin therapy.

Design: The PREVAIL study was a multicenter, prospective, randomized controlled study comparing the WATCHMAN Device to long-term warfarin therapy. A 2:1 randomization allocation ratio (two Device subjects to one Control subject) was used with stratification by center. Subjects were eligible to participate in PREVAIL if they were at least 18 years of age, had non-valvular atrial fibrillation and were eligible for long-term warfarin therapy with a $CHADS_2$ score of at least 2. Subjects with a $CHADS_2$ score of 1 were also permitted to enroll if they had any of the following characteristics (consistent with the recommendations presented in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation):

- The subject was female age 75 or older.
- The subject had a baseline LVEF ≥ 30% and < 35%.
- The subject was age 65-74 and had diabetes or coronary artery disease.
- The subject was age 65 or greater and had documented congestive heart failure.

A roll-in phase permitted physicians to gain experience with the WATCHMAN implant procedure. Subjects randomized to receive the WATCHMAN Device underwent TEE at 45 days, 6-, and 12-months after successful device implantation. Subjects randomized to the Control group were to remain on warfarin with INR monitoring every other week through 6 months and monthly thereafter. All randomized subjects underwent follow-up at 45 days, 6-, 9-, and 12-months, semiannually through 3 years and annually thereafter through 5 years.

This study had three primary endpoints:

- First primary endpoint: The 18-month rates of the composite of stroke (including hemorrhagic or ischemic), systemic embolism, and cardiovascular or unexplained death. The non-inferiority success criterion for the WATCHMAN group vs. the control group was a rate ratio of less than 1.75 with posterior probability of at least 97.5% (or equivalently that the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 1.75).
- Second primary endpoint: The 18-month rates of ischemic stroke or systemic embolism excluding the first 7 days post-randomization. The non-inferiority success criterion for the WATCHMAN group vs. the control group was either: (1) a rate ratio of less than 2.0, or (2) a rate difference of less than 0.0275, each with a posterior probability of at least 97.5% (or equivalently that (1) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 2.0 or (2) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate difference would be less than 0.0275).
- Third primary endpoint: The percentage of WATCHMAN subjects that experienced one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later: all-cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. The following events were not included in the assessment of this endpoint: percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat a femoral pseudoaneurysm, and non-surgical treatments of access site complications. The third primary endpoint event rate was compared to a performance goal of 2.67%.

A Bayesian approach based on a piecewise exponential model was used to evaluate the first and second primary endpoints based on time to first event. In addition, this approach included prior PROTECT AF historical data at 1,500 patient-years of follow-up from subjects with the same $CHADS_2$ enrollment criteria as the PREVAIL subjects with a discounting weight of 50%. For the third primary endpoint, a Bayesian approach based on a beta-binomial model was used to incorporate historical data from the PROTECT AF study and CAP registry through a prior distribution (without discounting) from subjects with the same $CHADS_2$ score enrollment criteria as the PREVAIL subjects.

Enrollment: The study enrolled 461 subjects with 407 randomized and the remaining 54 participating in the WATCHMAN roll-in group. Of the 407 randomized subjects, 269 were assigned to the WATCHMAN group and 138 assigned to the warfarin control group as shown in **Table 15**.

Table 15. PREVAIL Enrollment Summary

Group	N
WATCHMAN Group	
Randomized	269
Implant Attempt*	265
Implanted	252
No Implant Attempt	4
Control Group	
Randomized	138
Roll-in Group	
Enrolled	54
Implant Attempt*	54
Implanted	51
No Implant Attempt	0

*Implant attempt is defined as venous access.

Subject Demographics and Baseline Clinical Features: For subjects randomized to the WATCHMAN group, the mean $CHADS_2$ score was 2.6 ± 1.0, the mean CHA_2DS_2-VASc score was 3.8 ± 1.2, the mean age was 74 years, 68% were male, and 94% were Caucasian. For subjects randomized to the Control group, the mean $CHADS_2$ score was 2.6 ± 1.0, the mean CHA_2DS_2-VASc score was 3.9 ± 1.2, the mean age was 75 years, 75% were male, and 95% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Table 4** and **Table 6**.

Results: WATCHMAN Device implant success (defined as successful release of the device) was achieved in 252/265 (95%) subjects who underwent the implant procedure.

The term "PREVAIL Only" refers to data from subjects enrolled in the PREVAIL study without the prior PROTECT AF study information used in the Bayesian analysis.

The pre-specified analyses were based on the data available at 6 months following the completion of enrollment. When this was achieved in the January 2013 dataset, the PREVAIL Only subject mean follow-up post-randomization was 11.8 ± 5.8 months, and 113 of 407 (28%) randomized subjects reached or passed the window for their 18-month follow-up visit. Final follow-up was completed in October of 2017, with the PREVAIL Only subject mean follow-up was 49.4 months, and 272 of 407 randomized subjects completed the 5 year follow-up visit (**Table 16**).

Table 16. Total Patient-Years for PREVAIL-Only Subjects and Prior Data Borrowed from PROTECT AF With 50% Discount

Dataset	PREVAIL-Only data in pt-yrs			PROTECT AF Prior Information in pt-yrs		
	WATCHMAN	Control	Total	WATCHMAN	Control	Total
Pre-specified: January 2013	256.2	140.0	396.2	395.3	223.5	618.8
Final: October 2017 (final)	1119.5	556.42	1675.9	395.3	223.5	618.8

First Primary Endpoint: Results of the Bayesian analysis for the first primary endpoint of all stroke (ischemic and hemorrhagic), systemic embolism, and death (cardiovascular or unexplained) are shown in **Table 17**. The 18-month rate is the model-based probability of an event occurring within 18 months.

Table 17. PREVAIL First Primary Endpoint Results (Intent-to-Treat)

Bayesian Approach	WATCHMAN 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Posterior Probability of NI	Rate Ratio NI Criterion 95% CrI Upper Bound < 1.75 (Post Probability ≥ 97.5%)
Pre-specified: Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL-Only January 2013 Dataset (396.2 pt-yrs)	0.064	0.063	1.07 (0.57, 1.89)	95.69%	No
Final: Prior PROTECT AF PREVAIL-Only October 2017 Dataset (1626 pt-yrs)	0.066	0.051	1.33 (0.78, 2.13)	88.39%	No

CrI = credible interval, NI = non-inferiority

In the January 2013 pre-specified Bayesian analysis, the 18-month event rate was 0.064 for the WATCHMAN group and 0.063 for the control group. The Bayesian estimate for the 18-month rate ratio was 1.07 with a 95% credible interval of 0.57 to 1.89. Since the upper bound of 1.89 was not lower than the non-inferiority margin of 1.75 defined in the statistical analysis plan, the non-inferiority criterion was not met (the posterior probability of non-inferiority was 95.69%). At final follow-up, the Bayesian rate for the 18-month rate ratio was 1.33 with a 95% credible interval of 0.78 to 2.13. Since the upper bound of 2.13 was not lower than the 1.75 non-inferiority margin, the non-inferiority criterion was still not met (posterior probability of non-inferiority was 88.39%).

The primary effectiveness endpoint analysis from the final PREVAIL-Only subjects is shown as time to event in a Kaplan-Meier curve in **Figure 2.**

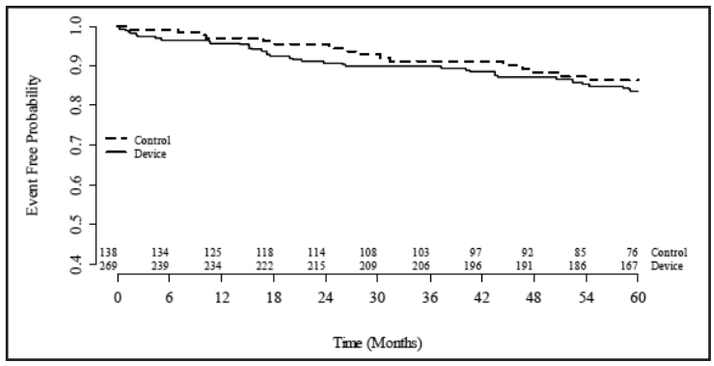


Figure 2. PREVAIL-Only Subjects – First Primary Endpoint Event

Table 18 shows the individual event rates of the composite endpoint for PREVAIL-Only subjects. The ischemic stroke rate (1.7 vs. 0.7 per 100 pt-years) favored the Control group, while the hemorrhagic stroke rate (0.2 vs. 0.5 per 100 pt-years) favored WATCHMAN, and death (cardiovascular or unexplained) rate (1.9 vs. 2.0 per 100 pt-years) was equivalent.

Table 18. PREVAIL Effectiveness Results and % of subjects who experienced 1 or more events – Final Dataset (PREVAIL-Only Subjects)

Randomization Allocation (2 Device: 1 Control)

	WATCHMAN		Control	
Component of First Primary Endpoint	**Event Rate (per 100 Pt-yrs)**	**N Events / Subjects (%)**	**Event Rate (per 100 Pt-yrs)**	**N Events / Subjects (%)**
Stroke - Ischemic	1.7 (18/1075)	18/269 (6.7%)	0.7 (4/547)	4/138
Stroke - Hemorrhagic	0.2 (2/1119)	2/269 (0.7%)	0.54 (3/554)	3/138
Systemic Embolism	0.1 (1/1116)	1/269 (7.8%)	0 (0/557)	0/138
Death (Cardiovascular or Unexplained)	1.9 (21/1119.5)	21/269 (7.8%)	1.9 (11/557)	11/138
Ischemic Stroke and Systemic Embolism	1.8 (19/1070.5)	19/269 (7.0%)	1.3 (7/543.2)	4/138
All stroke	1.9 (20/1073.9)	20/269 (7.4%)	0.7 (4/546.1)	7/138

Second Primary Endpoint: Results of the Bayesian analysis for the second primary endpoint are shown in **Table 19**. The 18-month rate is the model-based probability of an event occurring within 18 months.

Table 19. PREVAIL Second Primary Endpoint Results (Intent-to-Treat)

Bayesian Approach	WATCHMAN 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI) (Posterior Prob)	18-Month Rate Difference (95% CrI) (Posterior Prob)	Rate Ratio Non-Inferiority Criterion or Rate Difference Non-Inferiority Criterion 95% CrI Upper Bound < 0.0275
Pre-specified: Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL-Only January 2013 Dataset (396.2 pt-yrs)	0.0253	0.0200	1.6 (0.5, 4.2) 77.2%	0.0053 (-0.0190, 0.0273) 97.6%	Yes
Final: Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL-Only October 2017 Dataset (1626 pt-yrs)	0.0255	0.0135	2.2 (0.8, 4.9) 52.1%	0.0120 (-0.0036, 0.02748) 97.5%	Yes

CrI = credible interval

In the January 2013 pre-specified Bayesian analysis, the 18-month rate was 0.0253 for the WATCHMAN group and 0.0200 for the control group. The non-inferiority criterion was met for the rate difference of 0.0053 with an upper bound of 0.0273, which was less than the allowable 95% credible interval upper bound of 0.0275. The non-inferiority criterion was not met for the rate ratio of 1.6 with an upper bound of 4.2, which exceeded the allowable 95% credible interval upper bound of 2.0.

In the final Bayesian analysis, the 18-month rate was 0.0255 for the WATCHMAN group and 0.0135 for the control group. The non-inferiority criterion was met for the rate difference (0.0120 with an upper bound of 0.02748, which was less than the allowable 95% credible interval upper bound of 0.0275), with a posterior probability for non-inferiority of 97.5%. The non-inferiority criterion was not met for the rate ratio of 2.2 with an upper bound of 4.9, which exceeded the allowable 95% credible interval upper bound of 2.0 (posterior probability for non-inferiority of 52.1%).

The second effectiveness endpoint for the PREVAIL-Only subjects (final dataset) is shown as time to event analysis in a Kaplan Meier curve in **Figure 3**.

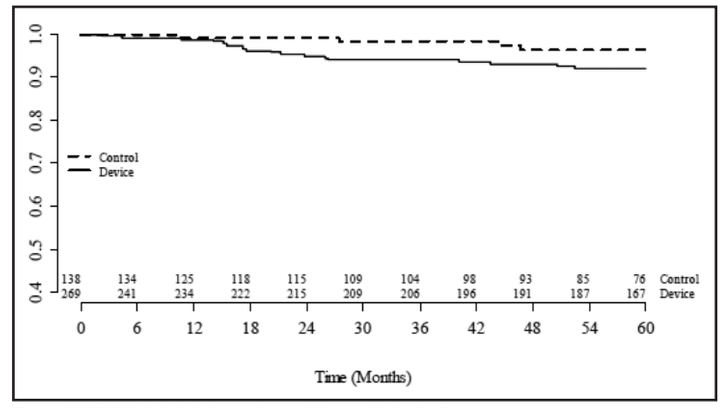


Figure 3. PREVAIL-Only Subjects – Second Primary Endpoint Event

Third Primary Endpoint: Of 269 PREVAIL-Only WATCHMAN subjects, 6 experienced a third primary endpoint event between the time of randomization and within 7 days of the procedure or by hospital discharge, corresponding to an event rate of 2.2% (**Table 20**).

Table 20. PREVAIL Third Primary Endpoint Results (Intent-to-Treat)

WATCHMAN Group		
N Subjects	**% (n/N)**	**95% CrI**
269	2.2% (6/269)	2.652%

CrI is one-sided, N = number, CrI = credible interval

Based on the Bayesian analysis incorporating prior information from PROTECT AF and CAP via a beta-binomial model, the one-sided 95% credible interval upper bound was 2.652%, which met the performance goal of 2.67%. The third primary endpoint events occurring in 6 PREVAIL-Only subjects are shown in **Table 21**.

Table 21. Third Primary Endpoint Events by Type of Initial Event (Intent-to-Treat)

PREVAIL-Only WATCHMAN™ Group N=269		
Type	**N Events**	**% of Subjects**
Device Embolization	2	0.7%
AV Fistula	1	0.4%
Cardiac Perforation	1	0.4%
Pericardial Effusion with Cardiac Tamponade	1	0.4%
Major Bleed Requiring Transfusion	1	0.4%

PREVAIL-Only Major Bleeding Analysis: The rates of major bleeding complications, defined as events adjudicated as serious adverse events, are shown in **Table 22**. There were more bleeding events in the WATCHMAN group immediately post-procedure through 45 days, an equivalent rate of bleeding through 6 months, and a lower rate 6 months post-procedure. The overall major bleeding rates were lower in the WATCHMAN group versus the Control Group.

Table 22. PREVAIL-Only Major Bleeding

	WATCHMAN		Control	
Major Bleeding	**N Events/ Subjects (%)**	**Rate per 100 Pt-yrs (N Events/ Total Pt-yrs)**	**N Events/ Subjects (%)**	**Rate per 100 Pt-yrs (N Events/ Total Pt-yrs)**
Procedure-related	12/269 (4.5%)	N/A	N/A	N/A
Non-procedure related	24/269 (8.9%)	2.3 (24/1051.4)	22/138 (15.9%)	4.3 (22/506.1)
0-45 days	7/269 (2.6%)	21.9 (7/32.0)	0/138 (0.0%)	0.0 (0/169)
46 days – 6months	6/269 (2.4%)	0.6 (6/1019.4)	3/138 (2.2%)	0.6 (3/489.2)
> 6 months	11/269 (4.8%)	1.2 (11/930.9)	19/138 (14.5%)	4.3 (19/438.8)
Total major bleeding	35/269 (13.0%)	3.5 (35/1012.6)	21/138 (15.2%)	4.1 (21/509.6)

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN and Control groups is presented in **Table 23**. Serious adverse events related to the WATCHMAN Device or implant procedure are shown in **Table 8**.

Table 23. PREVAIL-Only Serious Adverse Events

	WATCHMAN N=269				Control N=138			
Event Type	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**
AV Fistula	1	0.7	1	0.4	0	0	0	0
Anemia Requiring Transfusion	4	2.8	4	1.5	0	0	0	0
Bleeding, Other	0	0	0	0	2	3.1	2	1.4
Cardiac Perforation	1	0.7	1	0.4	0	0	0	0
Cranial Bleed	1	0.7	1	0.4	0	0	0	0
Death	42	29.6	42	15.6	29	44.6	29	21.0
Device Embolization	2	1.4	2	0.7	0	0	0	0
Device Thrombus	1	0.7	1	0.4	0	0	0	0
Endocarditis	1	0.7	1	0.4	0	0	0	0
Epistaxis	2	1.4	1	0.4	2	3.1	2	1.4
Gastrointestinal Bleeding	20	14.1	19	7.1	12	18.5	12	8.7
Hematoma	2	1.4	2	0.7	1	15	1	0.7
Hematuria	1	0.7	1	0.4	2	3.1	2	1.4
Infection	3	2.1	3	1.1	0	0	0	0
Major Bleed Requiring Transfusion	8	5.6	8	3.0	4	6.2	4	2.9
Other Study Related	7	4.9	6	2.2	1	1.5	1	0.7
Pericardial Effusion with Cardiac Tamponade	4	2.8	4	1.5	0	0	0	0
Pseudoaneurysm	1	0.7	1	0.4	0	0	0	0
Rectal Bleeding	2	1.4	2	0.7	1	1.5	1	0.7
Respiratory Failure	4	2.8	4	1.5	0	0	0	0
Respiratory Insufficiency	1	0.7	1	0.4	0	0	0	0
Stroke - Hemorrhagic	2	1.4	2	0.7	3	4.6	3	2.2
Stroke - Ischemic	20	14.1	18	6.7	6	9.2	4	2.9
Subdural Hematoma	2	1.4	2	0.7	0	0	0	0
Systemic Embolism	1	0.7	1	0.4	0	0	0	0
Transient Ischemic Attack (TIA)	9	6.3	8	3.0	2	3.1	2	1.4

PREVAIL-Only Device Thrombus Rates

The device thrombus-related stroke rate was 0.3 events per 100 patient-years as shown in **Table 24.**

Table 24. PREVAIL-Only Device-related Thrombus

	N=252
Thrombus Subjects	16 (6.4%)
Thrombus Events	17
Experienced Ischemic Stroke	3
Experienced Serious Adverse Event	5
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.3

Discontinuation of warfarin among WATCHMAN subjects: Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 92% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

CAP Registry

Primary Objective: To collect additional safety and effectiveness data on the WATCHMAN Device in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy.

Design: The CAP registry was a multi-center prospective non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Up to 30 investigative centers with prior WATCHMAN Device experience in the PROTECT AF study were allowed to participate. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation, have a $CHADS_2$ score of 1 or greater, and be eligible for long-term warfarin therapy. Following baseline evaluation and device implantation, subjects were seen at 45 days, at 6-, 9-, and 12-month visits, and semi-annually thereafter through 5 years.

The endpoints of the CAP registry were identical to those in the PROTECT AF study, but there were no pre-defined statistical hypotheses. The primary effectiveness endpoint was the rate of the composite of stroke (including ischemic and hemorrhagic), systemic embolism, and cardiovascular death (cardiovascular or unexplained). The primary safety endpoint was the rate of life-threatening events as determined by the CEC, which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion, and any bleeding related to the device or procedure that necessitated a surgical procedure.

Enrollment: A total of 26 centers (24 U.S., 2 European) participated by enrolling at least one subject. A total of 566 subjects were enrolled. The average $CHADS_2$ score was 2.5 ± 1.2, the mean CHA_2DS_2-VASc score was 3.9 ± 1.5, the mean age was 74 years, and 66% of subjects were male as shown in **Table 4** and **Table 6**.

The CAP Registry is complete. Follow-up of the 566 subjects was 2293 patient-years.

Results: The WATCHMAN Device was successfully implanted in 534/566 (94%) subjects. For the primary effectiveness endpoint, a rate of 3.1 events/100 patient-years was observed, with cardiovascular or unexplained death and ischemic stroke being the two most common events over a mean follow-up duration of 50.1 months as shown in **Tables 25** and **26**. The primary safety rate was 3.1 events per 100-patient years.

Table 25. CAP Primary Effectiveness Endpoint (2293 Patient Years)

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI
Primary Effectiveness	3.1 (70/2292.5)	2.4, 3.9
Primary Safety	3.1 (66/2160.9)	2.4, 3.9

Table 26. CAP Effectiveness Results and % of subjects who experienced 1 or more events

	Event Rate (per 100 Pt-yrs)	N Events/ Subjects (%)
Stroke - Ischemic	1.30 (30/2300.1)	5.3% (30/566)
Stroke - Hemorrhagic	0.17 (4/2359.1)	0.7% (4/566)
Systemic Embolism	0.04 (1/2359.8)	0.2% (1/566)
Death (Cardiovascular or Unexplained)	1.69 (40/2363.2)	6.2% (35/566)

CAP Major Bleeding Analysis: The rates of major bleeding complications, defined as events adjudicated as serious adverse events, are shown in **Table 27**.

Table 27. CAP Major Bleeding

WATCHMAN		
Major Bleeding	**N Events/ Subjects (%)**	**Rate per 100 Pt-yrs (N Events/ Pt-yrs)**
Procedure-related	18/566 (3.2%)	N/A
Non-procedure related	68/566 (12.0%)	3.1 (68/2179.2)
0-45 days	14/566 (2.5%)	20.4 (14/68.6)
46 days – 6 months	14/566 (2.5%)	0.7 (14/2110.6)
> 6 months	40/566 (8.0%)	2.1 (40/1918.8)
Total major bleeding	81/566 (14.3%)	3.8 (81/2125.0)

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN is presented in **Table 28**. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in **Table 8**.

Table 28. CAP Registry Serious Adverse Events

Event	Number of Events	Number of Subjects	% of Subjects N=566
Death	101	101	17.8%
Stroke - Ischemic	34	30	5.3%
Stroke - Hemorrhagic	5	4	0.7%
Systemic Embolization	1	1	0.2%
Gastrointestinal Bleeding	73	46	8.1%
Other Study Related	22	20	3.5%
Transient Ischemic Attack (TIA)	14	12	2.1%
Major Bleed Requiring Transfusion	9	8	1.4%
Pericardial Effusion with Cardiac Tamponade	7	7	1.2%
Anemia Requiring Transfusion	5	4	0.7%
Pericardial Effusion	5	5	0.9%
Pseudoaneurysm	5	5	0.9%
Prolonged Bleeding from a Laceration	3	3	0.5%
Cranial Bleed	1	1	0.2%
Epistaxis	2	2	0.4%
Hematuria	2	2	0.4%
Ventricular Tachyarrhythmia	2	2	0.4%
Arrhythmias	1	1	0.2%
Bruising - Hematoma	1	1	0.2%
Cardiac Perforation	1	1	0.2%
Chest Pain/ Discomfort	1	1	0.2%
Device Embolization	1	1	0.2%
Device Thrombus	1	1	0.2%
Rectal Bleeding	1	1	0.2%

CAP Device Thrombus Rates: The device thrombus-related stroke rate was 0.1 events per 100 patient-years as shown in **Table 29**.

Table 29. CAP Device-related Thrombus

	N=534
Thrombus Subjects	14 (2.6%)
Thrombus Events	21
Experienced Ischemic Stroke	2
Experienced Serious Adverse Event	10
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.1

Discontinuation of warfarin among WATCHMAN subjects: Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 96% discontinued warfarin therapy by 45 days, and 96% discontinued warfarin therapy by 12 months.

CAP2 Registry

Primary Objective: To collect additional safety and effectiveness data on the WATCHMAN Device in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy.

Design: The CAP2 Registry is a multi-center prospective non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Up to 60 investigative centers with prior WATCHMAN experience in the PREVAIL study were allowed to participate. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation, be eligible for long-term warfarin therapy, and have a $CHADS_2$ score of at least 2. Subjects with a $CHADS_2$ score of 1 were also permitted to enroll if they had any of the following characteristics (consistent with the recommendations presented in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation):

- The subject was female age 75 or older.
- The subject had a baseline LVEF ≥ 30% and < 35%.
- The subject was age 65-74 and had diabetes or coronary artery disease.
- The subject was age 65 or greater and had documented congestive heart failure.

Following baseline evaluation and device implantation, subjects were seen at 45 days, 6- and 12-month visits, and semi-annually through 3 years and annually thereafter through 5 years.

The endpoints of the CAP2 registry were similar to those used in the PREVAIL study, but there were no pre-defined statistical hypotheses. There were three primary endpoints (two effectiveness and one safety) as follows: 1) the rate of the composite of stroke (including hemorrhagic and ischemic), systemic embolism, and cardiovascular or unexplained death; 2) the rate of the composite of ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following device implantation; and 3) the occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever was later.

Demographics: A total of 47 U.S. investigational sites actively participated by enrolling at least one subject in the study. A total of 576 subjects were enrolled. The average $CHADS_2$ score was 2.7 ± 1.1, the mean CHA_2DS_2-VASc score was 4.5 ± 1.3, the mean age was 75 years, and 61% of subjects were male as shown in **Table 4** and **Table 6**.

Values presented are mean ± standard deviation, n (minimum, maximum) or number of subjects/total number of subjects (%) as appropriate.

The CAP Registry is complete. Follow-up of the 576 subjects was 2329 patient-years.

Table 30. CAP2 First Primary Endpoint (2329 Patient Years)

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
4.8 (107/2220.5)	(4.0, 5.8)

Table 31. CAP2 Effectiveness Results and % of subjects who experienced 1 or more events

	Event Rate (per 100 Pt-yrs)	% (N Events/ Subjects)
Stroke - Ischemic	2.2 (49/2230.0)	8.5% (49/576)
Stroke - Hemorrhagic	0.1 (2/2322.2)	0.3% (2/576)
Systemic Embolism	0.1 (2/2324.3)	0.3% (2/576)
Death (Cardiovascular or Unexplained)	2.9 (68/2329.6)	12.0% (69/576)

Second Primary Endpoint: A rate of 2.2 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 50.3 months as shown in **Table 32** and **Table 33**.

Table 32. CAP2 Second Primary Endpoint (2329 Patient Years)

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
2.2 (49/2227.0)	(1.7, 2.9)

Table 33. CAP2 Events Contributing to Second Primary Endpoint

Endpoint Event Type	N Events	% of Subjects N=576
Stroke - Ischemic	53	8.1%
Systemic Embolism	2	0.3%

Third Primary Endpoint: Eight subjects experienced a third primary endpoint event between time of enrollment and within 7 days of procedure or by hospital discharge corresponding to an event rate of 1.4% as shown in **Table 34** and **Table 35.**

Table 34. CAP2 Third Primary Endpoint

N Subjects	% (n/N)	95% CI
576	1.4% (8/576)	(0.6%, 2.7%)

Table 35. CAP2 Events Contributing to Third Primary Endpoint

Type	N Events	% of Subjects N=576
Cardiac Perforation	3	0.5%
Death	1	0.2%
Major Bleeding Requiring Transfusion	1	0.2%
Myocardial Infarction	1	0.2%
Stroke (Ischemic)	1	0.2%
Valvular Damage	1	0.2%

Serious Adverse Events: A summary of all adjudicated serious adverse events for the WATCHMAN is presented in **Table 36**. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in **Table 8.**

Table 36. CAP2 Registry Serious Adverse Events

Type	N Events	% (N Pts with Event/ 576) N=576
Anemia Requiring Transfusion	11	1.4% (8/576)
Pericardial Effusion with Cardiac Tamponade	8	1.4% (8/576)
Subdural Hematoma	8	1.4% (8/576)
Hematoma	7	1.0% (6/576)
Death - Non-Cardiovascular	76	13.2% (76/576)
Death - Cardiovascular/ Unexplained	68	11.8% (68/576)
Cranial Bleed	6	1.0% (6/576)
Stroke (Ischemic)	51	7.8% (45/576)
Rectal Bleeding	5	0.9% (5/576)
Cardiac Perforation	3	0.5% (3/576)
Myocardial Infarction	3	0.5% (3/576)
Ventricular Fibrillation	3	0.5% (3/576)
Pseudoaneurysm	3	0.5% (3/576)
Major Bleed Requiring Transfusion	32	4.3% (25/576)
Device Thrombus (thrombus on the atrial facing side of the device)	25	3.6% (21/576)
Other (Non-Study Related)	31	5.4% (31/576)
Gastrointestinal Bleeding	25	3.8% (22/576)
Oral Bleeding	2	0.3% (2/576)
Bleeding, Other	2	0.3% (2/576)
Respiratory Insufficiency	2	0.3% (2/576)
Stroke (Hemorrhagic)	2	0.3% (2/576)
Systemic Embolism	2	0.3% (2/576)
Infection	3	0.5% (3/576)
Respiratory Failure	20	3.5% (20/576)
Other (Study Related)	14	2.4% (14/576)
Pericardial Effusion	13	2.3% (13/576)
Epistaxis	12	1.6% (9/576)
Hematuria	10	1.6% (9/576)
Transient Ischemic Attack (TIA)	12	2.1% (12/576)
Bleeding from Varicose Veins	1	0.2% (1/576)
Hemothorax	1	0.2% (1/576)
Valvular Damage	1	0.2% (1/576)
Arrhythmias	1	0.2% (1/576)

CAP2 Device Thrombus Rates: The device thrombus-related stroke rate was 0.2 events per 100 patient-years as shown in **Table 37**.

Table 37. CAP2 Device-related Thrombus

	N=545
Thrombus Subjects	21 (3.9%)
Thrombus Events	25
Experienced Ischemic Stroke	4
Experienced Serious Adverse Event	6
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.2

Discontinuation of warfarin among WATCHMAN subjects: The CAP2 Registry is ongoing and data collection is ongoing. Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 93% discontinued warfarin therapy by 45 days, and 97% discontinued warfarin therapy by 12 months.

NESTed Surveillance Analysis Plan (SAP)

Primary Objective: To assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN Left Atrial Appendage (LAA) Closure Technology in a routine clinical setting.

Design: The WATCHMAN New Enrollment PoST Approval Surveillance Analysis Plan (NESTed SAP) is a multi-center, prospective, non-randomized registry utilizing data captured in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR). Two cohorts of 1,000 patients (primary and secondary) will be included in the analysis. The Primary Cohort will consist of subjects who are eligible for a WATCHMAN Device according to current U.S. indications with a calculated $CHADS2_2$score of ≥ 2 or a CHA_2DS_2-VASc score of ≥ 3 and exclude any patients who are contraindicated for a WATCHMAN Device according to this document or patients with concomitant cardiac or non-cardiac procedures (including, but not limited to: cardiac ablation, trans-catheter valve implantation, coronary intervention, etc.). Once the primary cohort is complete, the next consecutive 1,000 patients implanted will be included in the secondary cohort.

The pre-specified primary efficacy endpoints will only be applied to the primary cohort and are as follows: 1) the rate of stroke (including

ischemic and/or hemorrhagic), all-cause death and systemic embolism at 24 months, 2) the rate of ischemic stroke or systemic embolism at 24 months as adjudicated by the Clinical Events Adjudication Team. The formal analysis of these endpoints will take place after all patients have completed the 24-month follow-up.

The Primary Safety event rate is calculated as the percent of all implanted or attempted patients who experience a Primary Safety event, defined as occurrence of one of the following events between the time of first implant procedure and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint. Events related to subsequent WATCHMAN implant procedures are also excluded from this endpoint.

Demographics: A total of 1,000 subjects were enrolled in the primary cohort. The mean $CHADS_2$ score was 3.2 ± 1.2, the mean CHA_2DS_2- VASc score was 5.0 ± 1.4, the mean HAS-BLED score was 2.7 ± 1.1, the mean age was 76.5 years, and 62% of subjects were male as shown in **Table 4** and **Table 6**.

The NESTed SAP is ongoing. Current follow-up of the primary cohort is a median of 12 months and 838.9 patient-years.

Results: The WATCHMAN Device was successfully implanted in 947/993 (95%) subjects. The first and second primary endpoint will be evaluated after all patients complete 2 years of follow-up.

Third Primary Endpoint: Fifteen subjects experienced a third primary endpoint event between time of enrollment and within 7 days of procedure or by hospital discharge corresponding to an event rate of 1.5% as shown in **Table 38** and **Table 39**.

Table 38. NESTed Third Primary Endpoint

N Subjects	% (n/N)	95% CI
1000	1.5% (15/1000)	2.3%

N = number, CI = confidence interval

The one-sided 95% confidence interval upper bound was 2.3%, which met the performance goal of 3.36% (p=0.0002). The 17 third primary endpoint events that occurred in 15 NESTed Subjects are shown in **Table 39**.

Table 39. Third Primary Endpoint Events by Type of Initial Event (Intent-to-Treat)

NESTed Primary Cohort N=1000		
Type	**N Events**	**% of Subjects**
Pericardial Effusion (requirement open cardiac surgery)	1	0.1%
Death*	4	0.4%
Ischemic stroke	2	0.2%
Surgery (unspecified)	5	0.5%
Systemic Thromboembolism (other than stroke)	2	0.2%
Retroperitoneal Bleeding	3	0.3%

*The 4 deaths were adjudicated as follows: 2 pulmonary, 1 stroke, and 1 sudden cardiac death.

NESTed-DAPT Surveillance Analysis

Primary Objective: The primary objective of this registry study was to assess safety outcomes associated with the use of dual antiplatelet therapy (DAPT) instead of warfarin and aspirin as the immediate post-implant anti-thrombotic regimen for the WATCHMAN Left Atrial Appendage (LAA) Closure Technology in a routine clinical setting.

Design: NESTed-DAPT was a prospective, observational, propensity-matched comparative analysis utilizing data captured in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR) between October 2018 and June 2019.

Key eligibility criteria include a calculated CHA_2DS_2-VASc score of ≥ 2 in men and ≥ 3 in women, effective LAA occlusion with a WATCHMAN Device (LAA leak ≤ 5 mm), no concomitant cardiac or non-cardiac procedures, and discharged either with DAPT (DAPT cohort) or a combination of warfarin and aspirin (Control cohort).

The NESTed-DAPT analysis had two Co-Primary Endpoints:

- Ischemic Stroke Performance Goal (ISPG) Endpoint: The 97.5% one-sided upper confidence limit of the observed Ischemic Stroke event rate between the date of hospital discharge and 45-days post-procedure for the DAPT Cohort must be ≤ 1.4%.
- Composite Endpoint (non-inferiority analysis): The composite event rate of all-cause death, stroke (ischemic and/or hemorrhagic), major bleed, and systemic embolism between date of hospital discharge and 45-days post-procedure.

Both Co-Primary Endpoints were evaluated using Propensity Score Matched subjects (PSM Primary Cohort) to adjust for differences in baseline covariates.

Demographics: The PSM Primary Cohort consisted of 2072 patients (1036 DAPT, 1036 Control), with mean ages 77.0±7.6 years (DAPT) and 77.1±7.0 years (Control), mean CHA_2DS_2- VASc score 5.1±1.5 (DAPT) and 5.0±1.3 (Control), and mean HAS-BLED score 2.7±1.0 for both DAPT and Control. Additional baseline demographics and characteristics are shown in **Table 4** and **Table 6** above.

Results:

ISPG Endpoint: The Primary Ischemic Stroke Performance Goal (ISPG) Endpoint for the Propensity Score Matched (PSM) Primary Cohort was met. The results are presented in **Table 40**.

Table 40: ISPG – WATCHMAN 2.5 PSM Primary Cohort (N=1036)

Event (Between Date of Discharge and 45-days Post-Procedure)	DAPT (N=1036)	One-Sided 97.5% Upper Confidence Limit*	Performance Goal	P-Value
Ischemic Stroke	0.10% (1/1036)	0.54%	1.4%	< .001

*The confidence limit for the binomial proportion is from Clopper-Pearson (Exact) method.

Composite Endpoint: The Composite Endpoint failed to meet the predetermined non-inferiority margin. The results are shown in **Table 41**.

Table 41. Composite Endpoint – WATCHMAN 2.5 PSM Primary Cohort (N=2072)

Composite Endpoint (Between Date of Discharge and 45-days Post-Procedure)	DAPT (N=1036)	Control (N=1036)	Difference [One-Sided 97.5% Upper Confidence Limit]	Margin	P-Value
All-Cause Death, Stroke (Ischemic and/ or Hemorrhagic), Major Bleed, Systemic Embolism	3.86% (40/1036)	2.51% (26/1036)	1.35% [2.91%]	2.6%	0.058

*The Farrington-Manning test is used to test the hypothesis of non-inferiority in the difference between the rates of the two treatment groups.

Table 42 presents a comparison of the components of the composite endpoint between the two cohorts. In the PSM Primary Cohort, device-related thrombus (DRT) rate was 0.29% (3/1036) in the DAPT group and 0% (0/1036) in the Control group.

Table 42: Components of Composite Endpoint – WATCHMAN 2.5 PSM Primary Cohort (N=2072)

Events* (Between Date of Discharge and 45-days Post Procedure)	DAPT (N=1036)	Control (N=1036)
All-Cause Death	0.77% (8/1036)	0.48% (5/1036)
All Stroke	0.10% (1/1036)	0.19% (2/1036)
Ischemic Stroke	0.10% (1/1036)	0.00% (0/1036)
Hemorrhagic Stroke	0.00% (0/1036)	0.19% (2/1036)
Systemic Embolism	0.19% (2/1036)	0.10% (1/1036)
Major Bleed	2.80% (29/1036)	1.83% (19/1036)

*All Events except 'All-Cause Death' were Adjudicated by ACCF.

Post-Hoc Analyses - WATCHMAN Gen 2.5

Post-hoc analyses were performed on all patients in the Control Cohort (N=4134) and DAPT Cohort (N=1047) with and without quintiles propensity score stratification. **Table 43** presents the outcomes for the same two endpoints. **Table 44** presents a comparison of the components of the composite endpoint between the two cohorts

Table 43: Composite Endpoint – WATCHMAN 2.5 Unmatched Analyses and Quintiles Propensity Score Matched Analyses (N=5181)

Primary Composite Endpoint* (Between Date of Discharge and 45-days Post-Procedure)	DAPT (N=1047)	Control (N=4134)	Difference (One-Sided 97.5% Upper Bound)
Unmatched Primary Composite Endpoint	3.82% (40/1047)	3.41% (141/4134)	0.41% [1.92%]
Quintiles Propensity Score Matched Primary Composite Endpoint	4.2%	3.5%	0.71% [2.27%]

* Composite of all-cause mortality, stroke, major bleeding, and systemic embolism.

Table 44: Components of Composite Endpoint – WATCHMAN 2.5 Unmatched Primary Cohort (N=5181)

Events* (Between Date of Discharge and 45-days Post-Procedure)	DAPT (N=1047)	Control (N=4134)
All-Cause Death	0.76% (8/1047)	0.73% (30/4134)
All Stroke	0.10% (1/1047)	0.22% (9/4134)
Ischemic Stroke	0.10% (1/1047)	0.10% (4/4134)
Hemorrhagic Stroke	0.00% (0/1047)	0.12% (5/4134)
Systemic Embolism	0.19% (2/1047)	0.05% (2/4134)
Major Bleed	2.77% (29/1047)	2.56% (106/4134)

*All Events except 'All-Cause Death' were Adjudicated by ACCF.

Post-Hoc Analyses – WATCHMAN FLX

At the time of this analysis, WATCHMAN FLX has mostly replaced WATCHMAN 2.5 in the US market. To assess the use of DAPT after implantation of WATCHMAN FLX, the same analysis was repeated with new WATCHMAN FLX patient data obtained from the LAAO Registry. The analysis included all WATCHMAN FLX LAAO Registry patients between August 2020 and June 2021 who met the same NESTed-DAPT eligibility criteria. Based on the discharge anti-thrombotic regimen, the endpoints were evaluated in 1461 DAPT subjects and 1741 Control subjects who completed the 45-day follow-up visit.

The WATCHMAN FLX Primary Cohort had mean ages 77.1±7.6 years (DAPT) and 76.5±7.6 years (Control), mean CHA_2DS_2- VASc score 5.1±1.5 (DAPT) and 4.9±1.5 (Control), mean HAS-BLED score 2.6±1.0 (DAPT) and 2.6±1.1 (Control), female 40.8% (DAPT) and 39.1% (Control), and Caucasian 91.6% (DAPT) and 94.9% (Control). Additional baseline demographics and characteristics are shown in **Tables 5** and **7** above.

In the WATCHMAN FLX cohort, ischemic stroke occurred in 0.3% (4/1461) DAPT patients and 0.2% (3/1741) Control patients. **Tables 45** and **46** present the overall composite endpoint results and by component endpoint events, respectively. Device-related thrombus (DRT) rate was 0.2% (3/1461) in the DAPT Cohort and 0.1% (2/1741) in the Control Cohort.

Table 45. Composite Endpoint Result– WATCHMAN FLX Primary Cohort (N=3202)

Composite Endpoint (Between Date of Discharge and 45-days Post-Procedure)	DAPT (N=1461)	Control (N=1741)	Difference [One-Sided 97.5% Upper Confidence Limit]
All-Cause Death, Stroke (Ischemic and/or Hemorrhagic), Major Bleed, Systemic Embolism	4.2% (62/1461)	3.4% (60/1741)	0.80% [2.2%]

Table 46: Components of Composite Endpoint Results – WATCHMAN FLX Primary Cohort (N=3202)

Events* (Between Date of Discharge and 45-days Post Procedure)	DAPT (N=1461)	Control (N=1741)
All-Cause Death	1.0% (15/1461)	1.0% (17/1741)
All Stroke**	0.4% (6/1461)	0.3% (6/1741)
Ischemic Stroke	0.3% (4/1461)	0.2% (3/1741)
Hemorrhagic Stroke	0.2% (3/1461)	0.2% (3/1741)
Systemic Embolism	0.0% (0/1461)	0.0% (0/1741)
Major Bleed	3.1% (46/1461)	2.6% (45/1741)

*All Events except 'All-Cause Death' were Adjudicated by ACCF.

**1 DAPT subject had both 1 Ischemic Stroke and 1 Hemorrhagic Stroke

Conclusion:

The NESTed-DAPT Primary Ischemic Stroke Performance Goal (ISPG) Endpoint (WATCHMAN 2.5) was met with a PSM Primary DAPT ischemic stroke rate of 0.10%. The upper one-sided confidence limit was 0.54%, which was below the prespecified performance goal of 1.40% (P< 0.001). The WATCHMAN 2.5 NESTed-DAPT analysis demonstrated that a DAPT regimen following WATCHMAN LAAO is associated with an acceptable risk of ischemic stroke. Similarly low 45-day ischemic stroke rates were observed across the post hoc WATCHMAN 2.5 and WATCHMAN FLX datasets.

The pre-specified NESTed-DAPT Composite Endpoint was not met. The observed composite endpoint rate difference between the two groups was driven mainly by the difference in major bleeding (2.80% DAPT vs 1.83% Control).

Additional post-hoc analyses performed with WATCHMAN Gen 2.5 and the WATCHMAN FLX data did not identify a signal for excessive major bleeding with DAPT. The observed difference in major bleeding in the WATCHMAN 2.5 PSM Primary Cohort may reflect an imbalance on unmeasured covariates of future bleeding risks between the groups.

The NESTed-DAPT study was designed to assess safety outcomes associated with the use of dual antiplatelet therapy (DAPT) instead of OAC as the immediate post-implant medication regimen for the WATCHMAN FLX Left Atrial Appendage (LAA) Closure Technology in a routine clinical setting. The totality of real-world clinical data from patients receiving DAPT therapy following WATCHMAN 2.5 and WATCHMAN FLX implantation support that DAPT is a reasonable alternative post-implant medication regimen.

PINNACLE FLX Study

Primary Objective: The primary objective of this study is to establish the safety and effectiveness of the WATCHMAN FLX Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation who are eligible for non-vitamin K antagonist oral anticoagulation (NOAC) therapy to reduce the risk of stroke.

Design: PINNACLE FLX is a prospective, non-randomized, multi-center investigation to establish the safety and effectiveness of the WATCHMAN FLX LAA Closure Device for subjects with non-valvular atrial fibrillation who are eligible for anticoagulation therapy to reduce the risk of stroke but have a rationale to seek a non-pharmacologic alternative.

Main study entry criteria included, but were not limited to, at least 18 years of age with non-valvular atrial fibrillation, be eligible for short-term OAC therapy, and have a CHA_2DS_2-VASc score of at least 2 for males and 3 for females. Following baseline evaluation and device implantation, subjects are seen at 45 days, at 6-, 12-, 18-, and 24-month visits. Implanted subjects underwent TEE at 45 days and 12-month visits. Investigators include physicians with WATCHMAN implant experience. Sites were limited to two implanting investigators per institution. All sites were required to enroll two roll-in subjects prior to enrollment in the main cohort of subjects.

The study had two primary endpoints:

1) Effectiveness: the rate of effective LAA closure defined as any peri-device leak ≤ 5 mm demonstrated by TEE at 12 months; and

2) Safety: the occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention between the time of implant and 7 days following the procedure or by hospital discharge, whichever was later.

Enrollment: The study enrolled 508 subjects at 29 investigational centers in the United States between May 7, 2018 and November 9, 2018. Of these, 29 subjects failed the screening, and 21 subjects met the clinical eligibility criteria but did not undergo an implant. Of the remaining 458 subjects, there were 400 main cohort subjects and 58 roll-in subjects.

The PINNACLE FLX study is complete. Average follow-up of the 400 main cohort patients was 12.8 months at the time of the primary analysis. The 2-year follow-up visit occurred in 96.6% of the patients.

The PINNACLE FLX follow-up attendance is presented in **Table 47**.

Table 47. Visit Compliance Main Cohort

Visit	All Enrolled Subjects(N=400)
45-day	100.0% (400/400)
6-month	96.1% (370/385)
12-month	96.0% (356/371)
18-month	96.1% (341/355)
24-month	96.6% (337/349)
Values presented are % (# visits observed / # visits expected).	

Demographics and Baseline Clinical Features: The mean age of the main cohort was 73.8 ± 8.6 years, 35.5% were female, and 93.7% were Caucasian. The mean CHA_2DS_2-VASc score was 4.2 ± 1.5, and the mean HAS-BLED score was 2.0 ± 1.0.

Results: The WATCHMAN FLX Device was successfully implanted in 395/400 (98.8%) subjects who underwent the implant procedure.

Effectiveness: The primary efficacy endpoint is the rate of effective LAA closure defined as any peri-device leak ≤ 5 mm demonstrated by TEE at 12 months. The primary efficacy endpoint was met with a rate of 100% (lower one-sided 95% CI = 99.1%), which was above the performance goal of 97%. These results are summarized in **Table 48**. At 45-day follow-up, 100% of subjects (389/389) exhibited adequate LAA closure. **Table 49** reports the rate of effective LAA closure (peri-device leak ≤ 5 mm demonstrated by TEE) at implant, 45-day and 12-month.

Table 48: Primary Effectiveness Endpoint

Event	Event Rate (n/N)	Lower 1-sided 95% Confidence Interval	P Value
Primary effectiveness endpoint	100.0% (342/342)	99.1%	< 0.0001

Table 49: LAA Closure (per Core Laboratory assessment)

Peri-device Leak	Implant	45 Days	12 Months
Jet size 0 ≤ 5 mm	100.0% (376/376) [99.0%, 100.0%]	100.0% (389/389) [99.1%, 100.0%]	100.0% (344/344) [98.9%, 100.0%]
Jet size > 0 and ≤ 5 mm	7.4% (28/376) [5.0%, 10.6%]	17.2% (67/389) [13.6%, 21.4%]	10.5% (36/344) [7.4%, 14.2%]
Complete seal (i.e., Jet Size = 0 mm)	92.6% (348/376) [100%]	82.8% (322/389) [100%]	89.5% (308/344) [100%]
Jet size > 5 mm	0.0% (0/376) [0.0%, 1.0%]	0.0% (0/389) [0.0%, 0.9%]	0.0% (0/344) [0.0%, 1.1%]
TEE deemed not evaluable for leak by Core Laboratory*	2.3% (9/385) [1.1%, 4.4%]	0.8% (3/392) [0.2%, 2.2%]	0.9% (3/347) [0.2%, 2.5%]

Data are % (n/N) [min, max]

*Site evaluation of TEEs assessed peri-device flow as < 5 mm in all cases.

Safety: The primary safety endpoint was met with a rate of 0.5% (upper one-sided 95% CI=1.6%), which was below the performance goal of 4.21% (This is equivalent to Third Primary Endpoint from PREVAIL and CAP2). These results are summarized in **Table 50**. Two ischemic stroke events occurred within 7 days of the implant procedure. The Secondary Effectiveness Endpoint is the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. **Table 51** shows the event rate for the Secondary Effectiveness Endpoint at 24 months. The secondary endpoint was met with a 24-month ischemic stroke or systemic embolism rate of 3.4%. This is below the prespecified performance goal of 8.7% (upper one-sided 95% confidence limit was 5.3%; P<0.001).

Table 50: Primary Safety Endpoint

Event	Event Rate (n/N)	Upper 1-sided 95% Confidence Interval	P Value
Primary safety endpoint	0.5% (2/400)	1.6%	< 0.0001

Table 51: Secondary Effectiveness Endpoint

Event	*Event Rate (n/N)*	*Upper 1-sided 95% log-log Confidence Bound*	*P Value*
Ischemic Stroke or Systemic Embolism rate at 2-years	*3.4% (13/400)*	*5.3%*	*< 0.001*

Major Clinical Events: The CEC adjudicated all major clinical events, including: all-cause stroke and TIA, systemic embolism, all-cause death, major bleeding events (BARC 3 or 5), device embolization, device thrombus, and pericardial effusion resulting in an invasive intervention. A summary of CEC adjudicated Major Clinical Events reported through the time of data cutoff is presented in **Table 52**.

Table 52: PINNACLE FLX Major Clinical Events*

Event	Number of Events	Number of Subjects with an Event
All-cause death	36	36
Cardiovascular/Unknown Death	21	21
All stroke	15	13
Ischemic stroke	14	12
Hemorrhagic stroke	1	1
Transient Ischemic Attack (TIA)	2	2
Systemic Embolism	1	1
Device Embolization	0	0
Device Thrombus	7	7
Pericardial Effusion (PE) resulting in invasive intervention	5	5
PE requiring open cardiac surgery	0	0
PE requiring pericardiocentesis or pericardial puncture	4	4
Major Bleeding (BARC 3 or 5)	44	39
BARC 3 bleeding	42	37
BARC 5 bleeding	2	2

* Please note, due to differences in methodologies for event adjudication and for assessment of device/procedure relatedness among the studies, the results of PINNACLE FLX (**Table 52**) are not directly comparable to the results of the studies in **Table 8**.

Table 53: Oral Anticoagulant (OAC) Use (Post-Implant through 45 Days)

OAC	Percent of Total % (n/N)
Apixaban	76.7% (303/395)
Rivaroxaban	20.3% (80/395)
Dabigatran	2.0% (8/395)
Warfarin/VKA[a]	0.5% (2/395)
Edoxaban	0.3% (1/395)
None[a]	0.3% (1/395)

[a]Documented as a protocol deviation

PINNACLE FLX Major Bleeding Analysis: The rates of major bleeding events, defined as CEC adjudicated BARC 3 or 5 bleeding, are shown in **Table 54**.

Table 54. PINNACLE FLX Major Bleeding

	WATCHMAN FLX	
Major Bleeding	**N Events/ Subjects (%)**	**Rate Per 100 Pt-yrs (N Events/ Total Pt-yrs)**
Procedure-related	1% (3/400)	0.4 (3/710.7)
Non-procedure related	9% (36/400)	5.1 (36/710.7)
0-45 days	2% (9/400)	1.3 (9/710.7)
46 days – 6 months	4% (16/400)	2.3 (16/710.7)
> 6 months	2.8% (11/400)	1.5 (11/710.7)
Total major bleeding	9.8% (39/400)	5.5 (39/710.7)

Device or Procedure-Related Serious Adverse Events: A summary of device or procedure-related serious adverse events is presented in **Table 55**.

Table 55. Device or Procedure-Related Serious Adverse Events

	All Device or Procedure Related Events	
Type	**Events**	**% Subjects with Events**
Anemia requiring transfusion	1	0.3% (1/400)
Arrhythmias	2	0.3% (1/400)
Death*	1	0.3% (1/400)
Device thrombus atrial facing – Post procedure	7	1.8% (7/400)
Fluid Overload	1	0.3% (1/400)
Gastrointestinal	1	0.3% (1/400)
Gastrointestinal bleeding	1	0.3% (1/400)
Peri-device leak[a]	10	2.5% (10/400)
Pericardial effusion	3	0.8% (3/400)
Prolonged bleeding from a laceration	1	0.3% (1/400)
Pulmonary	2	0.5% (2/400)
Respiratory insufficiency	1	0.3% (1/400)
Stroke (ischemic)	9	1.8% (7/400)
Systemic embolism	1	0.3% (1/400)
TEE/TTE related event	1	0.3% (1/400)
Thrombocytopenia	1	0.3% (1/400)
Total	**43**	**8.5% (34/400)**

Abbreviations: TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

Device and procedure relationship were primarily based on site assessment; this evaluation could be changed based on CEC assessment. Individual n's may not add to total N if subject experienced multiple events.

[a]Core Laboratory evaluation of TEEs assessed peri-device leak as ≤ 5 mm in all cases.

*Cause of death (133 days following procedure): ischemic stroke. Autopsy revealed premortem thrombus on the surface of the left atrial appendage closure device.

PINNACLE FLX Device Thrombus Rates: The device-related thrombus stroke rate was 0.14 events per 100 patient-years as shown in **Table 56**

Table 56. PINNACLE FLX Device-related Thrombus

	N=400
Thrombus Subjects	7 (1.8%)
Thrombus Events	7
Experienced Ischemic Stroke	1
Experienced Serious Adverse Event	2
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.14

Discontinuation of NOAC among WATCHMAN FLX subjects: Among subjects successfully implanted with the WATCHMAN FLX Device and followed for at least 12 months, 96.2% discontinued NOAC therapy by 45 days.

ICE-LAA Study

Primary Objective: The primary objective of this study is to assess the use of intracardiac echocardiography (ICE) imaging of the left atrial appendage during implant of the WATCHMAN FLX Left Atrial Appendage Closure (LAAC) Device.

Design: The ICE-LAA study is a prospective, non-randomized, single-arm, multi-center investigation to assess the use of ICE imaging of the left atrial appendage during implant of the WATCHMAN FLX Left Atrial Appendage Closure (LAAC) Device.

Main study entry criteria included, but were not limited to: at minimum legal age per local geography to participate in the study, have non-valvular atrial fibrillation, and have a CHA_2DS_2-VASc score of at least 2. Following baseline evaluation and device implantation, subjects were seen at 45-days. Implanted subjects underwent TEE at 45 days. Investigators included physicians with WATCHMAN implant experience, as well as experience in performing commercial WATCHMAN implants using ICE.

The Primary Endpoint of the ICE LAA study is the rate of significant leak (>5 mm) at the 45-day post-implant TEE as assessed by the echocardiographic core laboratory.

Enrollment: The study enrolled 100 subjects at 7 investigational centers in Europe (Denmark, UK, Italy, and Spain) between July 2020 and September 2021. All subjects underwent an implantation procedure, however 2 subjects withdrew from the trial prior to the 45-day follow-up visit. The trial is now complete.

Demographics and Baseline Clinical Features: The mean age of the main cohort was 75.8 ± 7.7 years and 33.0% were female. The mean CHA_2DS_2-VASc score was 4.0 ± 1.5, and the mean HAS-BLED score was 2.0 ± 0.9.

Results:

The primary endpoint of the ICE LAA study was significant leak (>5mm). The rate of significant leak observed in the ICE LAA study was 0.0%, as shown in **Table 57.** The rates of effective closure of the LAA are shown post-procedure and at 45-days in **Table 58.** The CEC adjudicated all major clinical events, including all-cause stroke and TIA, systemic embolism, all-cause death, major bleeding events (BARC 3 or 5), device embolizations, device thrombus, and pericardial effusions resulting in an invasive intervention. A summary of CEC adjudication Major Clinical Events through 45-days post-procedure are presented in **Table 59.** Following use of ICE imaging during implant of the WATCHMAN FLX device there was 100% device success and technical success, as shown in the Procedural Outcomes in **Table 60.** Medications used post-procedure through 45 days are reported in **Table 61.**

Table 57. ICE-LAA Primary Endpoint

Event	Event Rate (n/N)	Upper 1-sided 97.5% Confidence Interval
Primary endpoint – Significant Leak (>5 mm)	0.0% (0/75)	4.8%

Table 58. LAA Closure (per Core Laboratory Assessment)

LAA Seal	Post-procedure (N=100)	45-Day Follow-up (N=76)*
Complete Seal	98.5% (66/67) [92.0%, 100.0%]	74.7% (56/75) [63.3%, 84.0%]
Jet Size ≤5mm	1.5% (1/67) [0.0%, 8.0%]	25.3% (19/75) [16.0%, 36.7%]

LAA Seal	Post-procedure (N=100)	45-Day Follow-up (N=76)*
Jet Size >5mm	0.0% (0/67) [0.0%, 5.4%]	0.0% (0/75) [0.0%, 4.8%]
Residual Flow not Assessed	0.0% (0/100) [0.0%, 3.6%]	0.0% (0/76) [0.0%, 4.7%]
Not evaluable	33.0% (33/100) [23.9%, 43.1%]	1.3% (1/76) [0.0%, 7.1%]

*If more than one measure assessed for the same subject, the one closest to the window (45 days) was considered.

N (denominator) based on the number of subjects with imaging data available during each period.

Table 59. CEC-Adjudicated Major Clinical Events at 45 days Post-procedure

Event	Event Rate
All-cause Mortality	1.0% (1/96)
Cardiovascular	1.0% (1/96)
Stroke	0.0% (0/96)
Ischemic	0.0% (0/96)
Hemorrhagic	0.0% (0/96)
Transient ischemic attack	0.0% (0/96)
Systemic embolism	0.0% (0/96)
Major bleeding (BARC 3 or 5)	3.1% (3/96)
BARC 3	3.1% (3/96)
BARC 5 (Fatal bleeding)	0.0% (0/96)
Clinically-relevant pericardial effusion	0.0% (0/96)
Device-related thrombus	0.0% (0/96)
Device migration	0.0% (0/96)
Device embolization	0.0% (0/96)

Table 60. Procedural Outcome

Measure	Subjects (N=100)
Device Successfully Deployed and Released	100% (100/100)
Device Success*	100% (100/100)
Technical Success**	100% (67/67)
Procedural Success***	96.0% (96/100)
Conversion to standard TEE during implant	0.0% (0/100)

*Device success – defined as implantation of a WATCHMAN FLX device without in-hospital mortality

**Technical success – defined as Device Successfully Deployed and Released, no conversion to TEE and effective closure of LAA at implant (no leak above 5mm).

***Procedural success – defined as device success plus absence of in-hospital device or procedure-related CEC adjudicated Events

Table 61. Oral Anticoagulation Use (Post-implant Through 45 Days)

Antiplatelet/Anticoagulant Medications	Subjects (N=100)
Post-implant	
Warfarin/VKA	2.0% (2/100)
NOAC (Dabigatran, Apixaban, Rivaroxaban, Edoxaban)	3.0% (3/100)
DAPT (2 antiplatelets together)	60.0% (60/100)
SAPT (1 antiplatelet)	25.0% (25/100)
None	10.0% (10/100)
45-day follow-up	
Warfarin/VKA	2.1% (2/95)
NOAC (Dabigatran, Apixaban, Rivaroxaban, Edoxaban)	2.1% (2/95)
DAPT (2 antiplatelets together)	50.5% (48/95)
SAPT (1 antiplatelet)	32.6% (31/95)
None	12.6% (12/95)

Post-implant: medication started and not stopped prior to implant OR medication started within 7 days post-implant.

45-day follow-up: medication started anytime(including prior to implant) up to 45 days and not stopped before 45 days post-implant

Abbreviations: DAPT=dual antiplatelet therapy; NOAC= non-VKA oral anticoagulants; SAPT=single antiplatelet therapy; VKA=vitamin K antagonist

HOW SUPPLIED

- The WATCHMAN FLX Pro Device is pre-loaded in the Delivery System.
- The Delivery System hemostasis valve is supplied in the closed position.
- The WATCHMAN FLX Pro Device with Delivery System is supplied STERILE using an ethylene oxide (EO) process.
- WATCHMAN Access Systems are packaged separately.

Device Details

- Do not use if package is damaged or unintentionally opened before use.
- Do not use if labeling is incomplete or illegible.

Handling and Storage

In storage, do not exceed 55 °C (131 °F). This product has no additional special handling or storage requirements.

OPERATIONAL INSTRUCTIONS

Preparation

A baseline measurement by means of appropriate imaging modality (either cardiac CT or TEE) should be performed to verify that a WATCHMAN FLX Pro Device may be implanted.

1. Perform the following through multiple imaging views:
   - Measure the LAA length and width at the ostium.
   - Assess LAA size/shape, number of lobes in LAA, and location of lobes to ostium.
   - Confirm the absence of thrombus.

Note: If using TEE, measure the LAA ostium at approximately these angles as anatomy permits:
- at 0° measure from coronary artery marker to a point approximately 2 cm from tip of the "limbus."
- at 45° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."
- at 90° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."
- at 135° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."

2. Determine the greatest width (i.e. diameter) measurement.
3. Record LAA ostium width and LAA depth measurements. Use **Table 57** as a guide for size selection. Measured maximum LAA ostium width must be ≥ 14.0 mm and ≤ 36.0 mm to accommodate available Closure Device sizes.

Note: Successful device sizing is dependent on multiple imaging views.

Note: Patient hydration can affect the size of the LAA.

Note: The maximum LAA ostium width and depth measurements determine Closure Device size selection.

PROCEDURE

Equipment Needed for Implantation Procedure

- Venous Introducer (optional)
- Standard transseptal access system
- 0.035 in (0.89 mm) guidewire (exchange length extra support)
- 5F (1.7 mm) or 6F (2.0 mm) angiographic pigtail catheter
- Any WATCHMAN Access System (which includes the Access Sheath and Dilator)

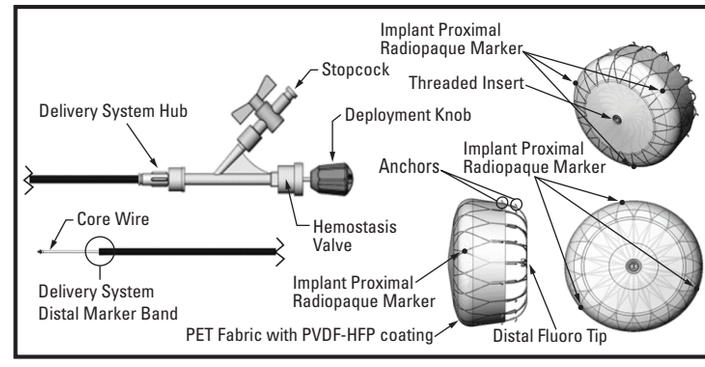


Figure 4. WATCHMAN FLX Pro Delivery System (Delivery Catheter and Closure Device)

Implantation Procedure

Note: Patients should start aspirin prior to scheduled procedure and continue daily.

Note: Fluoroscopic (fluoro) and echocardiographic imaging should be used when implanting the device.

Note: Patients should be fully heparinized throughout the procedure with a recommended minimum active clotting time (ACT) of 200 seconds - 300 seconds after transseptal puncture.

1. Use standard percutaneous techniques to puncture femoral vein and insert 0.035 in (0.89 mm) guidewire and vessel dilator. Use a standard, commercially available transseptal access system to cross inter-atrial septum.
2. Exchange crossing sheath with exchange length extra support 0.035 in (0.89 mm) guidewire. Position guidewire in left upper pulmonary vein (LUPV) or loop in left atrium.
3. Prepare a WATCHMAN Access System.

Note: Inspect sterile package and WATCHMAN Access System prior to use. If sterile barrier, labeling, packaging, or device have been compromised in any way, DO NOT USE.

A. Remove Access Sheath and Dilator from package under sterile conditions.
B. Inspect prior to use to ensure no damage.
C. Flush Access Sheath and Dilator with saline prior to use.
D. Ensure hemostasis valve is fully open. Insert Dilator into hemostasis valve of Access Sheath until the two snap together.

4. Advance a WATCHMAN Access System over guidewire into left atrium (LA). As the Access Sheath nears center of LA, unsnap the Access Sheath from the Dilator, hold the Dilator, and advance the Access Sheath into initial position in LA or ostium of LUPV.

Precaution: Use caution when introducing WATCHMAN Access System to prevent damage to cardiac structures.

5. Ensure hemostasis valve is fully open, remove Dilator and guidewire, leaving Access Sheath in LA or LUPV. Allow back bleed to minimize potential for introducing air before tightening valve. Flush the Access Sheath with saline.

   If continued back bleed is observed from the valve after the Dilator is removed despite attempting to close it, loosen the valve cap (counter clockwise rotation) until the cap spins freely. Then re-attempt closure of the valve while exerting gentle forward pressure on the valve cap during closure (clockwise rotation) to ensure proper engagement of the valve thread. While these steps are being undertaken, manual occlusion of the valve opening using a gloved finger is recommended to minimize blood loss.

Note: These steps may be repeated, if necessary. However, if this does not mitigate the blood leak, the user should remove and replace the WATCHMAN Access Sheath before proceeding with the procedure.

6. Carefully advance pigtail catheter through Access Sheath into distal portion of the LAA under fluoro guidance. Obtain angiographic views of the LAA.

Note: If user notices kink in WATCHMAN Access Sheath, user should remove and replace WATCHMAN Access Sheath before proceeding with procedure.

Note: Record multiple angles on cine with contrast prior to advancing the Access Sheath into LAA. Use fluoro guidance while advancing pigtail catheter and while advancing the Access Sheath. Stop if resistance is felt.

7. Confirm LAA size and select appropriate WATCHMAN FLX Pro Device. There is clinical evidence to support the use of TEE or intracardiac echocardiography (ICE) and fluoroscopy to guide LAAC implantation (see details in Clinical Studies section).

   A. Perform the following through multiple imaging views:
      - Measure the LAA length and width at the ostium.
      - Assess LAA size/shape, number of lobes, and location of lobes relative to the ostium.
      - Confirm the absence of thrombus.

Note: If using TEE, measure the LAA ostium at approximately these angles as anatomy permits:
- at 0° measure from coronary artery marker to a point approximately 2 cm from tip of the "limbus."
- at 45° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."
- at 90° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."
- at 135° measure from top of the mitral valve annulus to a point approximately 2 cm from tip of the "limbus."

Note: In the ICE-LAA study, physicians obtained at least two orthogonal (short axis and long axis) views of the LAA when using ICE from the left atrium to document the position, compression, leak, and record the tug test to comply with the PASS™ (Position, Anchor, Size, and Seal) device release criteria (refer to **Step 15**). These two views were further defined as:
- Short-Axis View (also called mid LA/PV view): with the ICE probe positioned in the mid LA, near or at the ostium of the left superior pulmonary vein. This resembles the 0-90° view on TEE.
- Long-Axis View (also called supra mitral view): a posterior flex, 90° rotation, and slight advancement of the probe toward the superior aspect of the mitral valve will delineate the long axis view of the LAA, which resembles the 90-135° view on TEE.

If using ICE imaging, visualize the LAA with the following anatomical structures: aortic valve (short-axis), mitral valve (long-axis), and pulmonary artery (short-axis), to assess the LAA anatomy, as well as the PASS criteria.

   B. Choose a Closure Device based on maximum LAA ostium width recorded. Use **Table 62** as a guide. The LAA depth should be approximately half the labeled Implant diameter or longer.

Note: LAA anatomy should accommodate a single Closure Device as described in **Table 62**.

Table 62. WATCHMAN FLX Pro Device Selection

Max LAA Ostium Width and/or Deployed Closure Device Diameter (mm)*	Closure Device Size (mm)
14.0 – 18.0	20
16.8 – 21.6	24
18.9 – 24.3	27
21.7 – 27.9	31
24.5 – 31.5	35
28.0 – 36.0	40

*The LAA depth should be approximately half the labeled Implant diameter or longer.

Note: These values are based on TEE and can be utilized with ICE. Other imaging modalities may vary.

8. Prepare WATCHMAN FLX Pro Delivery System.
   A. Check the temperature exposure indicator on the pouch label to confirm that the product has not been compromised. See Warnings section.
   B. Remove Delivery System under sterile conditions.

Note: Inspect sterile package and WATCHMAN Delivery System prior to use. If sterile barrier, labeling, packaging, or device have been compromised in any way, DO NOT USE.

Note: Delivery sheath hemostasis valve is packaged closed.

Precaution: Use caution when manipulating the Delivery System. Excessive counterclockwise rotation of the deployment knob or Delivery System hub independent from the rest of the Delivery System can cause premature implant detachment.

   C. Inspect prior to use to ensure there is no damage to hemostasis valve, catheter connections, or Closure Device (through Delivery System). Confirm the Closure Device is positioned completely inside the Delivery System.

Note: If Closure Device extends outside the Delivery System, DO NOT USE.

   D. Loosen the hemostasis valve and move the deployment knob away from the hemostasis valve to ensure the Closure Device and the core wire assembly move freely. While holding the Delivery System straight, position the distal tip of the Closure Device so that it is aligned with the Delivery System distal marker band.
   E. Flush the Delivery System and hemostasis valve with saline, to ensure removal of all air. Then close the hemostasis valve to maintain fluid throughout system during handling.

Note: If aspirating the Delivery System during flushing, do so slowly and with limited force, to prevent the formation of air bubbles.

9. With the pigtail in the LAA, the Access Sheath tip position and orientation may be carefully adjusted in the LAA as required to engage the target LAA lobe or location for deployment. Slowly remove pigtail catheter.
10. Loosen hemostasis valve of Access Sheath, allowing back bleed before inserting the prepped Delivery System. Apply positive pressure saline to the Delivery System flush port during introduction into Access Sheath to obtain a wet-to-wet connection.

Note: Tightening the Access Sheath hemostasis valve onto the WATCHMAN FLX Pro Delivery System may damage the Delivery System.

11. To avoid introduction of air, slowly advance Delivery System into Access Sheath under fluoro guidance.

Precaution: Use caution when introducing Delivery System to prevent damage to cardiac structures.

12. Under fluoro guidance, align Delivery System distal marker band with most distal marker band on Access Sheath. Once marker bands are aligned, stabilize Delivery System, retract Access Sheath, and snap together to create the Access Sheath/Delivery System Assembly.

Note: To inject contrast, a syringe or a manifold must be attached to the flush port of the Delivery System.

Precaution: If using a power injector, the maximum pressure should not exceed 690 kPa (100 psi).

13. To start the initial deployment of the WATCHMAN FLX Pro Closure Device, partially deploy the Closure Device by holding the deployment knob stationary while retracting the Access Sheath/Delivery System to form an Implant width approximately twice (2X) that of the WATCHMAN Access Sheath (see **Figure 5**). The Access Sheath/Delivery System Assembly can now be moved within the LAA, if necessary.

Note: WATCHMAN FLX Pro Device must be in this initial deployment configuration when advancing the Access Sheath/Delivery System Assembly into the LAA without a pigtail.

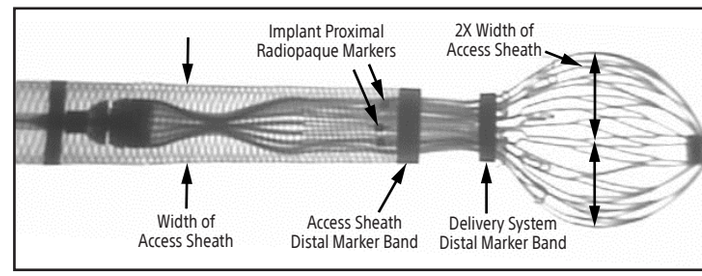


Figure 5. Initial deployment of the WATCHMAN FLX Pro Device showing the proper configuration of the Implant and Implant proximal radiopaque markers for positioning the Closure Device within the LAA.

14. To fully deploy the Closure Device with the Implant proximal RO markers (plane of maximum diameter) aligned at the LAA ostium, the Advancement Method, the Unsheathe Method, or a combination of both methods may be used during the deployment process:

    Advancement Method: Align the Delivery System distal marker band at the ostium, then advance the deployment knob forward relative to the Access Sheath/Delivery System Assembly to fully deploy the Closure Device.

    Unsheathe Method: Align the constrained Implant proximal RO markers to the ostium and retract the Access Sheath/Delivery System Assembly relative to the deployment knob to fully deploy the Closure Device.

    Immediately after the Closure Device is deployed, maintain slight forward pressure on the deployment knob of the Delivery System as the Implant expands and conforms to the LAA.

    Note: Just prior to full deployment of the Implant from the Delivery Catheter, the Implant proximal RO markers will align with the Delivery System distal marker band.

    Note: Adjustment of Access Sheath may be beneficial during deployment to achieve proper alignment of the Implant relative to the ostium.

    Note: Adjust Access Sheath to minimize influence of core wire on the Implant during PASS criteria assessment.

15. Closure Device release criteria: **P**osition, **A**nchor, **S**ize, and **S**eal (PASS criteria):

    A. **Position:** Plane of maximum diameter of the Closure Device should be at or just distal to the LAA ostium, where possible (see **Figure 7**), while meeting all other PASS criteria.

    If desired, fluoro position assessment confirmation can be performed by rotating the c-arm until the Implant proximal RO markers can be visualized in a straight line (see **Figure 6**).

    Note: The Implant proximal RO markers are not required to be evenly spaced.

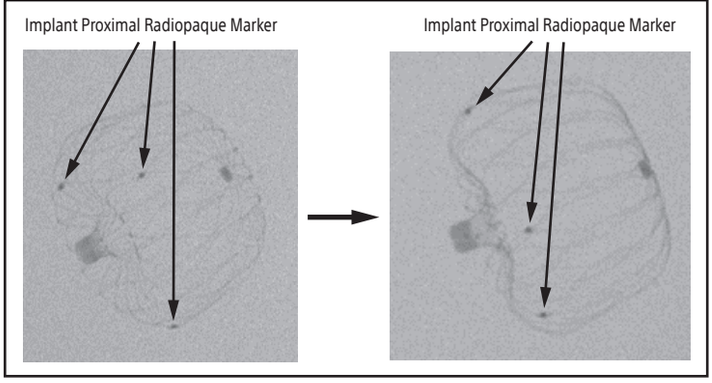


Figure 6. WATCHMAN FLX Pro Implant proximal Radiopaque marker alignment

Perform a contrast injection to visualize the ostium relative to the Implant proximal RO markers. Confirm the Implant proximal RO markers are at or distal to the ostium which validates that at least 2/3 of the Implant is inside the appendage.

Note: Closure Device position in relation to the LAA ostium may vary based on individual patient anatomy and the imaging view.

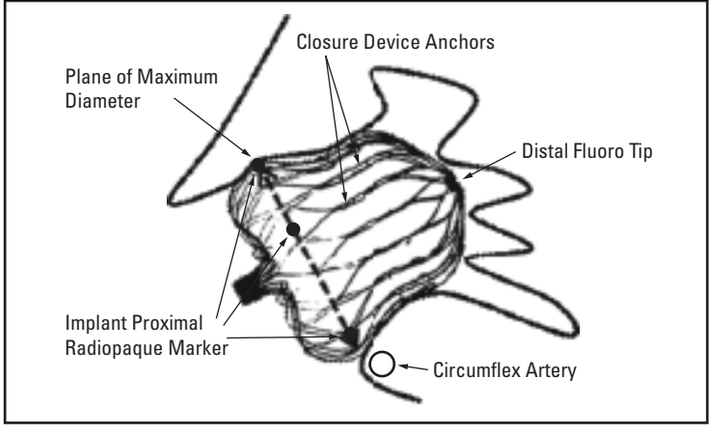


Figure 7. WATCHMAN FLX Pro Device Position and Size

B. **Anchor:** Move the tip of the Access Sheath back to expose sufficient core wire. Next, gently pull back on the deployment knob to visualize movement of the Closure Device and LAA together. The Implant proximal RO markers may be used as an indicator of Implant movement.

C. **Size (compression)**: Measure plane of maximum diameter of Closure Device (See **Figure 7**). Use **Table 62** as a guide.

D. **Seal:** Ensure all lobes are distal to Closure Device and sealed (i.e., no leak > 5 mm).

Note: If repositioning of the Closure Device is required, proceed to Step 16 (Closure Device repositioning). If removal of the Closure Device is required, proceed to Step 17 (Closure Device recapture and removal). If the Closure Device meets release criteria, proceed to Step 18 (Closure Device release).

16. If repositioning of the Closure Device is required, recapture the Closure Device per the following instructions.

    A. Advance tip of Access Sheath/Delivery System Assembly up to Closure Device and align Access Sheath/Delivery System Assembly with Closure Device (do not unsnap).

    B. Fix deployment knob position with right hand and gently advance Access Sheath/ Delivery System Assembly over the Closure Device by positioning the right thumb against the Delivery System hemostasis valve for stability and push the right thumb forward. Resistance will be felt as the Closure Device is collapsed into the Delivery System.

    C. Continue to advance the Access Sheath/Delivery System Assembly such that the Closure Device anchors are released from the LAA. The Closure Device may be fully recaptured into the Access Sheath/Delivery System Assembly as needed prior to redeployment. After recapture, the WATCHMAN FLX Pro Device may be repositioned using the guidance found in Step 13.

17. If removal of the Closure Device is required, recapture the Closure Device per the following instructions.

    A. Advance tip of Access Sheath/Delivery System Assembly up to face of Closure Device (do not unsnap).

    B. Fix deployment knob position with right hand and gently advance Access Sheath/ Delivery System Assembly over the Closure Device by positioning the right thumb against Delivery System hemostasis valve for stability and push the right thumb forward. Resistance will be felt as the Closure Device is collapsed into the Delivery System. Continue to advance the Assembly until Closure Device is completely collapsed, recaptured, and distal fluoro tip is proximal to the Delivery System Distal Marker Band. Tighten the Delivery System hemostasis valve.

    C. Ensure Access Sheath hemostasis valve is fully open. Unsnap Delivery System from Access Sheath while maintaining Access Sheath position. Slowly remove Delivery System.

    D. Insert pigtail catheter to reposition Access Sheath in LAA, if necessary.

    E. Repeat Steps 8-15 with new Delivery System.

18. If the Closure Device meets release criteria, release WATCHMAN FLX Pro Device.

    Warning: Do not release the WATCHMAN FLX Pro Device from the core wire if the Closure Device does not meet all release criteria (Step 15).

    A. Confirm proper Closure Device release criteria: **P**ositon, **A**nchor, **S**ize, and **S**eal (PASS criteria).

    B. Advance Access Sheath/Delivery System Assembly close to face of Closure Device.

    C. Rotate deployment knob counterclockwise 3-5 full turns.

    D. Confirm core wire is disconnected.

19. Ensure Access Sheath is free from anatomical structures prior to removal; adjust Access Sheath as necessary. Stop if resistance is felt.

20. Remove Access Sheath and Delivery System based on parameters for hemostasis.

21. Use standard of care for post-procedure bleeding at access site.

Disposal

To minimize the risk of infection or microbial hazards after use, dispose of device and packaging as follows:

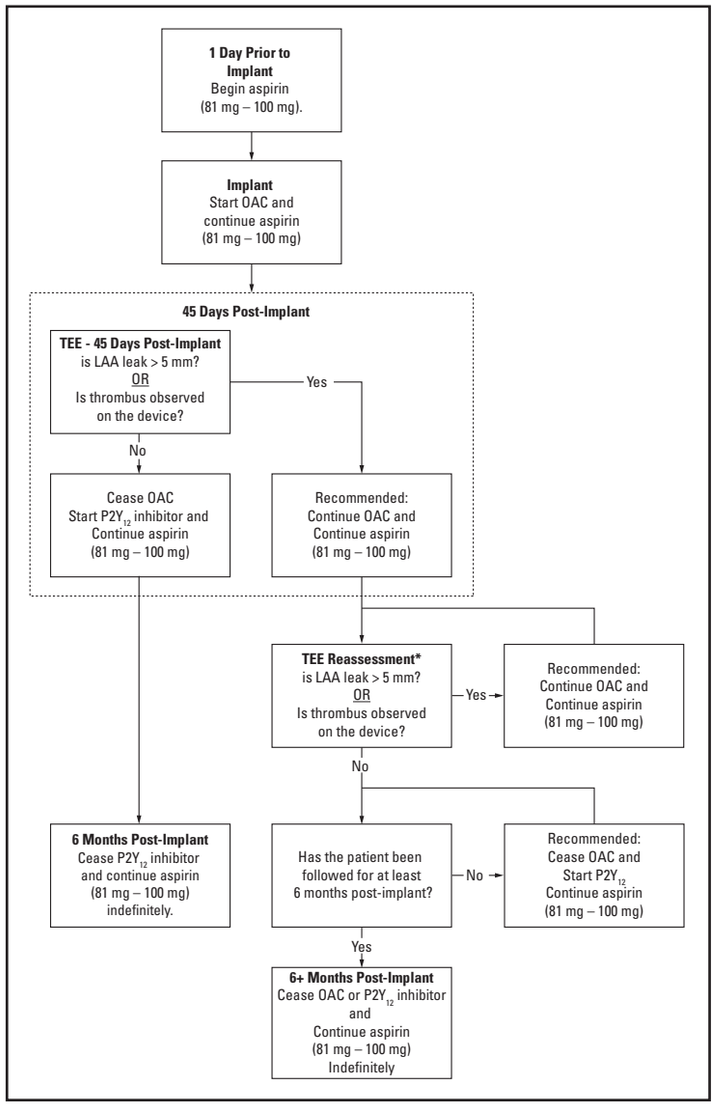
After use, device may contain biohazardous substances. The device and packaging should be treated and disposed of as biohazardous waste or have them treated and disposed of in accordance with any applicable hospital, administrative, and/or local government regulations. Use of a biohazardous container with biological hazard symbol is recommended. Untreated biohazardous waste should not be disposed of in the municipal waste system.

POST-PROCEDURE INFORMATION

Options for post-procedure antithrombotic therapy are shown below. Physicians should exercise clinical judgement based on individual patient characteristics in determining the most appropriate use of antithrombotic drugs for the post-implant medication regimen.

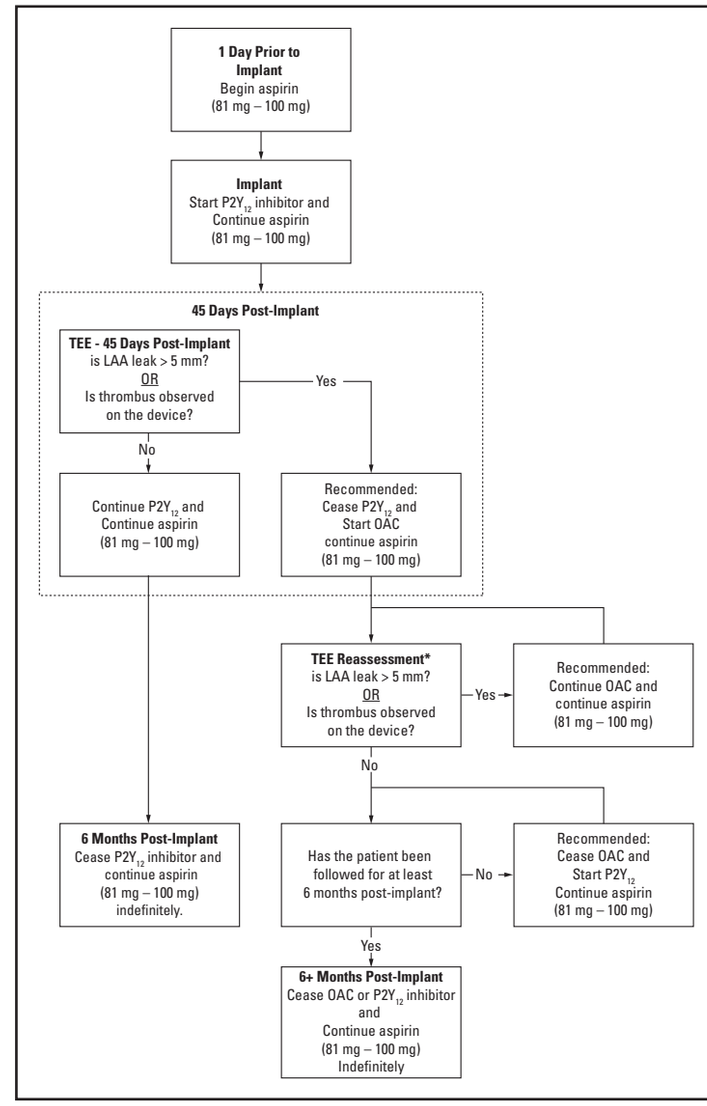
Option A) Short-term OAC (see Figure 8)

1. Patients should remain on 81 mg - 100 mg of aspirin. OAC therapy should be added post-implant. At 45 days (± 15 days) post-implant, perform WATCHMAN FLX Pro Device assessment with TEE. Cessation of OAC therapy is at physician discretion provided that any leak demonstrated is ≤ 5 mm. If adequate seal is not demonstrated, subsequent OAC therapy cessation decisions are contingent on demonstrating leak is ≤ 5 mm. At the time the patient ceases OAC therapy, the patient should continue aspirin and begin a $P2Y_{12}$ inhibitor daily. This regimen should continue until 6 months have elapsed after implantation. Patients should then remain on aspirin indefinitely. If a patient remains on OAC therapy and aspirin 81 mg - 100 mg for at least 6 months after implantation and then ceases OAC therapy, the patient should not require a $P2Y_{12}$ inhibitor but should continue aspirin daily.
2. At 45 days and at 12 months, perform imaging to assess the WATCHMAN FLX Pro Device with TEE.
   - Confirm absence of intra-cardiac thrombus.
   - Perform color Doppler assessment to include the device/LAA border at the following approximate TEE angles (0°, 45°, 90° and 135°). Measure any residual leak around the device into the LAA. If there is evidence of leak > 5 mm, continuing or restarting antigoagulation therapy is recommended.
   - If thrombus is observed on the device, use of anticoagulation is recommended until resolution of thrombus is demonstrated by TEE.
3. Prescribe appropriate endocarditis prophylaxis for 6 months following Closure Device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.



* The performance and timing of the LAA seal reassessment is left to physician discretion.

Figure 8. Option A) WATCHMAN FLX Pro Device Pharmacologic Regimen (Short-term OAC)



* The performance and timing of the LAA seal reassessment is left to physician discretion.

Figure 9. Option B) WATCHMAN FLX Pro Device Pharmacologic Regimen (DAPT-only)

Option B) DAPT-only (see Figure 9)

1. Patients should remain on 81 mg – 100 mg of aspirin. $P2Y_{12}$ inhibitor therapy should be added post-implant. At 45 days (± 15 days) post-implant, perform WATCHMAN FLX Pro Device assessment with TEE. $P2Y_{12}$ inhibitor therapy should continue for 6 months provided that any leak demonstrated is ≤ 5 mm. If adequate seal is not demonstrated, discontinuation of $P2Y_{12}$ and starting OAC is recommended. Subsequent OAC therapy cessation decisions are contingent on demonstrating leak is ≤ 5 mm. At the time the patient ceases OAC therapy, the patient should continue aspirin and re-start $P2Y_{12}$ inhibitor daily. This regimen should continue until 6 months have elapsed after implantation. Patients should then remain on aspirin indefinitely.
2. At 45 days and at 12 months, perform imaging to assess the WATCHMAN FLX Pro Device with TEE.
   - Confirm absence of intra-cardiac thrombus.
   - Perform color Doppler assessment to include the device/ LAA border at the following approximate TEE angles (0°, 45°, 90° and 135°). Measure any residual leak around the device into the LAA. If there is evidence of leak > 5 mm, discontinuation of $P2Y_{12}$ and starting OAC is recommended.
   - If thrombus is observed on the device, use of anticoagulation is recommended until resolution of thrombus is demonstrated by TEE.
3. Prescribe appropriate endocarditis prophylaxis for 6 months following Closure Device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

Any serious incident that occurs in relation to this device should be reported to Boston Scientific and the relevant local regulatory authority.

WARRANTY

For device warranty information, visit (www.bostonscientific.com/warranty). WATCHMAN, WATCHMAN FLX and PASS are trademarks of Boston Scientific Corporation or its affiliates.

SYMBOL DEFINITIONS

Commonly used medical device symbols that appear on the labeling are defined at www.bostonscientific.com/SymbolsGlossary.

Additional symbols are defined at the end of this document.

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