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WATCHMAN FLX™

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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 FLX 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 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 constrained within the Delivery System until deployment in the LAA. The WATCHMAN FLX Closure Device is compatible with all WATCHMAN Access Systems (Access Sheath and Dilator). The Closure Device is available in 5 sizes from 20 mm to 35 mm. Appropriate Closure Device sizing is determined by LAA measurements using fluoroscopy (fluoro), transesophageal echocardiographic, or intracardiac echocardiographic guidance.

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 Device is designed to be permanently implanted at or slightly distal to the ostium (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.

Contents

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

Materials

Materials and material amounts in the Closure Device are listed in Table 1 below. Materials are the same for all Closure Devices, but the amounts listed represent the 35 mm Closure Device, which contains the highest amount of each material.

Table 1. Closure Device Materials

Material	Amount(s)
Titanium Dioxide	0.000 4 g
Polyethylene terephthalate (PET)	0.094 g
Nickel-titanium alloy (Nitinol)	0.328 g
Titanium grade 2	0.031 g

Non-pyrogenic

This device meets pyrogen limit specifications.

USER INFORMATION

Intended Users of the WATCHMAN FLX 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 Physician Training program. The WATCHMAN FLX Physician Training program is a one-time training program; no re-training is required. Implantation of the WATCHMAN FLX Device should only be performed by these Intended Users.

INTENDED USE / INDICATIONS FOR USE

The WATCHMAN FLX 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 CHA₂DS₂-VASc¹ 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.

Following catheter ablation for non-valvular atrial fibrillation (concomitantly or sequentially with WATCHMAN FLX implantation):

The WATCHMAN FLX 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 CHA₂DS₂-VASc¹ scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy.

CONTRAINDICATIONS

Do not use the WATCHMAN FLX Device if:

- Intracardiac thrombus is present.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a Closure Device (see Table 67).
- 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 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 P2Y₁₂ inhibitor.

WARNINGS

Implantation of the WATCHMAN FLX 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 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 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 is red or missing, indicating Closure Device performance may have been compromised.
- Patients under deep or conscious sedation are at increased risk for having negative left atrial pressures, especially in the presence of hypovolemia or partial upper airway obstruction. Patients under positive pressure ventilation such as general anesthesia have reduced risk of negative atrial pressures. Negative left atrial pressures may increase the risk of air ingress through the hemostasis valve, particularly when the hemostasis valve is open while introducing, removing, or exchanging devices, which may result in air embolism. The most appropriate anesthesia method should be based on individual patient characteristics. Additional caution should be used with patients under deep or conscious sedation, such as:
 - Ensure the patient is not hypovolemic.
 - Make device exchanges with the hemostasis valve below the level of the heart or submerged in fluid, and withdraw devices slowly until the distal tip is near the valve, then make exchanges during expiration.

PRECAUTIONS

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN FLX Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The safety and effectiveness of the WATCHMAN FLX Device has not been established in patients with a left ventricular ejection fraction (LV EF) ≤30%.
- 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 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

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 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 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 Device is an option that may be considered in selected patients to reduce the risk of cardioembolism from the LAA.

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 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 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 Device implant pharmacologic regimen (see Post Procedure Information section) especially for patients at high risk for bleeding.

In considering the use of the WATCHMAN FLX Device (except in subjects who have undergone catheter ablation for non-valvular atrial fibrillation), 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.

Selection among available treatment options must first take into account whether anticoagulation is indicated to reduce the risk of stroke based on CHA₂DS₂-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 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.^{1,2,3}
- 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).

In considering the use of the WATCHMAN FLX device in subjects who have undergone catheter ablation for non-valvular atrial fibrillation, the following should be taken into account:

- The safety and effectiveness of the device compared to anticoagulation.
- Selection among available treatment options, including whether anticoagulation is indicated to reduce the risk of stroke based on CHA₂DS₂-VASC scores.
- 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).

PATIENT COUNSELING INFORMATION

Physicians should review the following information when counseling patients about the WATCHMAN FLX 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. **Table 8** and **Table 52** 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 following WATCHMAN FLX Device implantation.
- Clinical conditions may arise that require continuation or resumption of anticoagulation therapy following WATCHMAN FLX 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 Closure Device may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.	
Device Name	WATCHMAN FLX Closure Device
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	25 T/m (2,500 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 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 AntiPlatlet 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 were used in the WATCHMAN pivotal clinical trials for selection of device size.

¹ American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons. J Am Geriatr Soc. 2010 (http://www.americangeriatrics.org/files/documents/health_care_pros/JAGS.Falls.Guidelines.pdf)

² Seller MB, Newby LK. Atrial Fibrillation, Anticoagulation, Fall Risk, and Outcomes in Elderly Patients. Am Heart J. 2011; 161:241-246.

³ 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.

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	SURPASS Discharge Medications Sub-Analysis
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	An interim sub-analysis was designed to assess safety outcomes associated with the use of OAC alone as an alternative to an OAC and aspirin as the post-implant medication regimen for the WATCHMAN FLX.
Device	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN	WATCHMAN FLX	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	Non-randomized registry surveillance analysis

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	SURPASS Discharge Medications Sub-Analysis
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 Stroke event rate between the date of hospital discharge and 45-days post-procedure for the DAPT Cohort must be $\leq 1.4\%$.	1. Effectiveness: The rate of effective LAA closure defined as any peri-device leak ≤ 5 mm 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.	- Key safety endpoint: All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention within seven days of the procedure or by hospital discharge, whichever is later - Additional Endpoints: - At each LAAO Registry follow-up timepoint (discharge, 45 days, 6 months, and 12 months post-procedure): - Death - Stroke (Ischemic, Hemorrhagic) - Systemic embolism - Major bleeding
Number of Patients Enrolled	800 subjects 93 roll-in WATCHMAN 707 randomized 463 WATCHMAN 244 Control	566 WATCHMAN subjects	461 subjects 54 roll-in WATCHMAN 407 randomized 269 WATCHMAN 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	Discharge medication regimen: 23,404 NOAC alone 46,169 NOAC + aspirin 2303 Warfarin alone 6270 Warfarin + aspirin 8974 DAPT
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 Complete	Study Complete	Study Complete	Study Complete	Ongoing
Post Implant Drug Regimen	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	The SURPASS study is an observational, prospective, non-randomized, multicenter registry surveillance analysis. Post implant drug regimen was based on physician discretion
Scheduled Follow-Up Duration	5 years					45-days	2 years	45-days	2 years

* 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.

Table 4. Summary of OPTION Study

Patient Population	Following catheter ablation for non-valvular atrial fibrillation (concomitantly or sequentially with WATCHMAN FLX implantation), patients 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	OPTION
Purpose	The primary objective of this study was to determine if LAAC with the WATCHMAN FLX device was a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high-risk patients with NVAF.
Device	WATCHMAN FLX
Study Design	1:1 Randomized
Primary Endpoints	- Primary safety endpoint: Non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) through 36 months - Primary efficacy endpoint: Stroke (including ischemic and/or hemorrhagic), all-cause death, and systemic embolism at 36 months - Secondary endpoint: ISTH major bleeding (including procedural bleeding) at 36 months
Number of Patients Enrolled	106 Roll-in ablation + WATCHMAN FLX 803 randomized ablation + WATCHMAN FLX 797 randomized Control (ablation+ OAC)
Status of Subject Follow-Up	Study Complete
Post Implant Drug Regimen	WATCHMAN FLX arm: After implantation, WATCHMAN FLX patients were prescribed market-approved OAC and aspirin (75-100mg recommended) until the 3-month visit followed by aspirin until at least the 12-month visit. Aspirin was recommended for duration of the trial (3 years). Control arm: After randomization, patients continued or started market-approved OAC use per IFU for atrial fibrillation stroke prevention post catheter ablation and were required to remain on OAC for the duration of the trial (3 years).
Scheduled Follow-Up Duration	3 years

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 was 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 was 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 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 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 assessed 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) was 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) were included in the analysis. The Primary Cohort consisted of subjects who were eligible for a WATCHMAN Device according to current U.S. indications with a calculated CHADS₂ score of ≥2 or a CHA₂DS₂-VASC score of ≥3 and excluded any patients who were 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 CHA₂DS₂-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 was 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 were 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 ≤ 5mm 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 was a prospective, non-randomized, single-arm, multi-center investigation to assess the use of ICE imaging of the LAA during WATCHMAN FLX LAA 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.

SURPASS Discharge Medications Sub-analysis

The WATCHMAN FLX Device Surveillance Post Approval Analysis (SURPASS) is designed to assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN FLX LAA Closure Device with Delivery System in a routine clinical setting. Follow-up is ongoing. An interim sub-analysis was designed to assess safety outcomes associated with the use of non-vitamin K oral anticoagulant (NOAC) alone as an alternative to an oral anticoagulant (OAC) and aspirin as the post-implant medication regimen for the WATCHMAN FLX.

OPTION

OPTION was a prospective, randomized, multicenter, global investigation. Between June 11, 2019, and June 28, 2021, a total of 1600 patients underwent randomization at 106 sites in 10 countries. A total of 803 patients were randomized to catheter ablation + WATCHMAN FLX and 797 to ablation + OAC. The concomitant cohort was defined in the WATCHMAN FLX arm as concomitant ablation and LAAC occurring on the same day within 10 days of randomization (n=328). In the control arm, the concomitant cohort was defined as ablation within 10 days of randomization (n=326). The sequential cohort was defined in the WATCHMAN FLX arm as ablation 90 to 180 days before LAAC (n=475). In the control arm, the sequential cohort was defined as ablation occurring 90 to 180 days before randomization (n=471).

The primary objective of this study was to determine if LAAC with the WATCHMAN FLX device was a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high-risk patients with NVAF. The primary safety endpoint was non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) through 36 months. The primary effectiveness endpoint was the composite of stroke (including ischemic and/or hemorrhagic), all-cause death, and systemic embolism at 36 months. The secondary endpoint was ISTH major bleeding (including procedural bleeding) at 36 months.

Table 5. Summary of Baseline Demographics (WATCHMAN 2.5)

Characteristic	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP		NESTed-DAPT (WATCHMAN 2.5)		
	WATCHMAN N=463	Control N=244	P-value	WATCHMAN N=269	Control N=138	P-value			Primary Cohort N=1000	Secondary Cohort N=1000	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)	75.8±7.9 (43.0, 99.0)	77.0±7.6 (1036) (49.0, 95.0)	77.1±7.0 (1036) (52.0, 94.0)	0.876
Sex													

	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP		NESTed-DAPT (WATCHMAN 2.5)		
Characteristic	WATCHMAN N=463	Control N=244	P-value	WATCHMAN N=269	Control N=138	P-value			Primary Cohort N=1000	Secondary Cohort N=1000	DAPT N = 1036	Control N = 1036	P-value
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)	39.1% (391/1000)	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)	60.9% (609/1000)	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)	0.5% (5/1000)	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)	1.6% (16/1000)	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)	3.3% (33/1000)	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)	94.1% (941/1000)	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)	2.9% (29/1000)	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	0.3% (3/1000)	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)	0.4% (4/1000)	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)	0.873	42.8% (242/566)	53.6% (309/576)	46.7% (467/1000)	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)	32.0% (320/1000)	36.1% (361/1000)	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)	21.0% (210/1000)	18.6% (186/1000)	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	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)	0.3% (3/1000)	0.5% (5/1000)	0.2% (2/1036)	0.5% (5/1036)	0.452

Table 6. Summary of Baseline Demographics (WATCHMAN FLX)

Demographic	NESTed-DAPT (WATCHMAN FLX)			PINNACLE FLX N=400	ICE-LAA N=100	SURPASS Discharge Medications Sub-analysis				
	DAPT N = 1461	Control N = 1741	P-value			NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
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)	76.5 ± 7.96 (23404)	76.2 ± 7.75 (46169)	76.7 ± 7.99 (2303)	76.7 ± 7.69 (6270)	76.9 ± 8.01 (8974)
Sex										
Female	40.8% (596/1461)	39.1% (680/1741)	0.3176	35.5% (142/400)	33% (33/100)	45.31% (10605/23403)	40.60% (18742/46167)	45.59% (1050/2303)	39.44% (2473/6270)	41.63% (3736/8974)
Male	59.2% (865/1461)	60.9% (1061/1741)		64.5% (258/400)	67% (67/100)	54.69% (12798/23403)	59.40% (27425/46167)	54.41% (1253/2303)	60.56% (3797/6270)	58.37% (5238/8974)
Intersex	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Race/Ethnicity										
American Indian or Alaskan	0.2% (3/1461)	0.4% (7/1741)	0.3617	0.3% (1/382)	N/A	0.17% (40/22913)	0.22% (99/45491)	0.44% (10/2275)	0.19% (12/6194)	0.12% (11/8856)
Asian	1.5% (22/1461)	1.0% (17/1741)	0.1738	0.5% (2/382)	N/A	1.49% (342/22913)	0.98% (444/45491)	0.92% (21/2275)	0.77% (48/6194)	1.31% (116/8856)
Black/African American	5.7% (83/1461)	2.8% (48/1741)	<0.0001	4.7% (18/382)	N/A	3.95% (904/22913)	3.82% (1740/45491)	3.52% (80/2275)	3.04% (188/6194)	5.23% (463/8856)
Caucasian	91.6% (1339/1461)	94.9% (1653/1741)	0.0002	93.7% (358/382)	N/A	89.80% (20575/22913)	92.11% (41904/45491)	92.31% (2100/2275)	93.85% (5813/6194)	89.98% (7969/8856)
Hispanic/Latino	2.2% (32/1443)	2.6% (45/1732)	0.4876	2.6% (10/382)	N/A	4.35% (997/22913)	2.67% (1215/45491)	2.59% (59/2275)	2.02% (125/6194)	3.05% (270/8856)
Hawaiian/ Pacific Islander	0.0% (0/1461)	0.1% (2/1741)	0.5037	0.0% (0/382)	N/A	0.11% (25/22913)	0.09% (39/45491)	0.09% (2/2275)	0.05% (3/6194)	0.15% (13/8856)
Other	2.7% (39/1461)	2.4% (41/1741)	0.5702	0.0% (0/382)	N/A	0.13% (30/22913)	0.11% (50/45491)	0.13% (3/2275)	0.08% (5/6194)	0.16% (14/8856)
AF Pattern										
Paroxysmal AF	64.1% (932/1455)	57.7% (1004/1740)	0.0003	51.8% (207/400)	44.0% (44/100)	61.87% (14356/23205)	62.26% (28556/45864)	55.71% (1274/2287)	56.48% (3523/6238)	65.09% (5787/8891)

Demographic	NESTed-DAPT (WATCHMAN FLX)			PINNACLE FLX N=400	ICE-LAA N=100	SURPASS Discharge Medications Sub-analysis				
	DAPT N = 1461	Control N = 1741	P-value			NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Persistent AF	23.3% (339/1455)	24.1% (420/1740)	0.5790	36.5% (146/400)	15.0% (15/100)	21.18% (4915/23205)	21.73% (9966/45864)	19.94% (456/2287)	18.93% (1181/6238)	18.22% (1620/8891)
Permanent AF	12.6% (184/1455)	18.2% (316/1740)	<.0001	10.5% (42/400)	41.0% (41/100)	10.73% (2489/23205)	11.07% (5079/45864)	17.18% (393/2287)	18.40% (1148/6238)	11.51% (1023/8891)
Paced AF	N/A	N/A	N/A	1.3% (5/400)	N/A	N/A	N/A	N/A	N/A	N/A
Unknown	0.4% (6/1461)	0.1% (1/1741)	0.0523	N/A	0.0% (0/100)	N/A	N/A	N/A	N/A	N/A

Table 6. Summary of Baseline Demographics (WATCHMAN FLX), continued

Demographic	OPTION								
	Primary Analysis Intent-to-Treat (Combined Concomitant and Sequential Arms) (N=1600)			Concomitant Arm Subgroup (N=654)*			Sequential Arm Subgroup (N=946)†		
	WATCHMAN FLX (N=803)	Control (N=797)	P-value	WATCHMAN FLX (N=328)	Control (N=326)	P-Value	WATCHMAN FLX (N=475)	Control (N=471)	P=Value
Age, years	69.7±7.4 (803) (39.0, 86.0)	69.4±7.9 (797) (32.0, 87.0)	0.556	70.1±7.6 (328) (43.0, 86.0)	70.0±7.3 (326) (38.0, 87.0)	0.7363	69.3±7.2 (475) (39.0, 86.0)	69.1±8.3 (471) (32.0, 87.0)	0.6270
Sex									
Female	35.2% (283/803)	33.0% (263/797)	0.393	36.9% (121/328)	31.9% (104/326)	0.2551	34.1% (162/475)	33.8% (159/471)	0.9102
Male	64.8% (520/803)	66.9% (533/797)		63.1% (207/328)	67.8% (221/326)		65.9% (313/475)	66.2% (312/471)	
Intersex	0.0% (0/803)	0.1% (1/797)		0.0% (0/328)	0.3% (1/326)		0.0% (0/475)	0.0% (0/471)	
Race / Ethnicity									
American Indian or Alaskan	0.2% (2/803)	0.1% (1/797)	>0.999	0.0% (0/328)	0.3% (1/326)	0.4985*	0.4% (2/475)	0.0% (0/471)	0.4995*
Asian	0.5% (4/803)	0.1% (1/797)	0.374	0.3% (1/328)	0.0% (0/326)	1.0000*	0.6% (3/475)	0.2% (1/471)	0.6242*
Black/African American	1.7% (14/803)	1.4% (11/797)	0.558	2.4% (8/328)	0.3% (1/326)	0.0378*	1.3% (6/475)	2.1% (10/471)	0.3051
Caucasian	83.8% (673/803)	86.1% (686/797)	0.206	77.7% (255/328)	80.4% (262/326)	0.4096	88.0% (418/475)	90.0% (424/471)	0.3204
Hispanic/Latino	1.6% (13/803)	1.5% (12/797)	0.855	1.2% (4/328)	0.9% (3/326)	1.0000*	1.9% (9/475)	1.9% (9/471)	0.9855
Hawaiian/ Pacific Islander	0.0% (0/803)	0.0% (0/797)	Undef	0.0% (0/328)	0.0% (0/326)	Undef	0.0% (0/475)	0.0% (0/471)	Undef
Other	0.4% (3/803)	0.4% (3/797)	>0.999	0.0% (0/328)	0.3% (1/326)	0.4985*	0.6% (3/475)	0.4% (2/471)	1.0000*
AF Pattern									
Paroxysmal AF	59.4% (477/803)	62.9% (501/797)	0.156	48.8% (160/328)	43.3% (141/326)	0.1561	65.1% (309/475)	67.1% (316/471)	0.5079
Persistent AF	40.6% (326/803)	37.1% (296/797)		51.2% (168/328)	56.7% (185/326)	0.1561	34.9% (166/475)	32.9% (155/471)	0.5079
Permanent AF	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Paced AF	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Unknown	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*defined as concomitant ablation and LAAC within 10 days of randomization in the WATCHMAN FLX arm and as ablation within 10 days of randomization in the control arm

†defined as ablation 90 to 180 days before LAAC in WATCHMAN FLX patients and as ablation occurring 90 to 180 days before randomization in control patients

Table 7. Summary of Baseline Characteristics (WATCHMAN 2.5)

Characteristic	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP		NESTed-DAPT (WATCHMAN 2.5)		
	WATCHMAN N=463	Control N=244	P-value	WATCHMAN N=269	Control N=138	P-value			Primary Cohort N=1000	Secondary Cohort N=1000	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)	0.484	2.5 ± 1.2 (566) (1.0, 6.0)	2.7±1.1 (576) (1.0, 6.0)	3.2 ±1.2 (999) (0.0, 6.0)	3.0±1.3 (998) (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 ₂ DS 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 (999) (2.0, 9.0)	4.8±1.6 (998) (1.0, 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	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	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	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)	59.7% (344/576)	N/A	N/A	64.6% (669/1036)	66.3% (687/1036)	0.406

Characteristic	PROTECT AF			PREVAIL			CAP N=566	CAP2 N=576	NESTed SAP		NESTed-DAPT (WATCHMAN 2.5)		
	WATCHMAN N=463	Control N=244	P-value	WATCHMAN N=269	Control N=138	P-value			Primary Cohort N=1000	Secondary Cohort N=1000	DAPT N = 1036	Control N = 1036	P-value
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	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	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	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	2.0 ± 0.9 (576) (0.00, 5.00)	2.7±1.1 (997) (0.0, 6.0)	2.6±1.0 (999) (0.0, 7.0)	2.7±1.0 (1036) (0.0, 7.0)	2.7±1.0 (1036) (0.0, 6.0)	0.173

Table 8. Summary of Baseline Characteristics (WATCHMAN FLX)

Characteristic	NESTed-DAPT (WATCHMAN FLX)			PINNACLE FLX N=400	ICE-LAA N=100	SURPASS Discharge Medications Sub-analysis				
	DAPT N = 1461	Control N = 1741	P-value			NOAC Alone (N = 23404)	NOAC+ Aspirin (N=46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
CHADS ₂ Score (Continuous)	N/A	N/A	N/A	2.3 ± 1.2 (400) (0, 6.0)	N/A	N/A	N/A	N/A	N/A	N/A
CHA ₂ DS 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)	4.6 ± 1.50 (23357)	4.7 ± 1.48 (46087)	4.7 ± 1.51 (2296)	4.9 ± 1.47 (6261)	4.9 ± 1.52 (2523)
CHF	41.8% (611/1461)	41.3% (719/1741)	0.7650	32.3% (129/400)	13.0% (13/100)	35.36% (8272/23394)	36.11% (16662/46142)	41.36% (952/2302)	43.14% (2703/6265)	39.38% (3533/8971)
Hypertension	92.4% (1350/1461)	92.9% (1617/1741)	0.6075	86.0% (344/400)	79.0% (79/100)	90.79% (21245/23401)	91.55% (42260/46162)	90.75% (2090/2303)	92.23% (5781/6268)	92.15% (8269/8973)
Age 65-74	28.4% (415/1461)	31.8% (553/1741)	0.0393	35.8% (143/400)	31.0% (31/100)	N/A	N/A	N/A	N/A	N/A
Age ≥75	66.2% (967/1461)	63.1% (1098/1741)	0.0661	50.5% (202/400)	60.0% (60/100)	N/A	N/A	N/A	N/A	N/A
Diabetes	39.9% (583/1461)	38.3% (667/1741)	0.3574	30.5% (122/400)	27.0% (27/100)	32.42% (7585/23399)	34.30% (15829/46150)	34.87% (802/2300)	38.26% (2398/6268)	37.20% (3336/8968)
Previous stroke, TIA, or TE	36.6% (535/1461)	32.8% (571/1741)	0.0235	22.3% (89/400)	26.0% (26/100)	N/A	N/A	N/A	N/A	N/A
Vascular disease	60.2% (880/1461)	54.5% (949/1741)	0.0011	55.3% (221/400)	35.0% (35/100)	41.86% (9794/23398)	52.01% (24007/46157)	43.63% (1004/2301)	53.97% (3383/6268)	56.43% (5063/8972)
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)	2.5 ± 1.10 (23357)	2.8 ± 1.12 (46069)	2.7 ± 1.15 (2298)	3.1 ± 1.16 (6259)	3.0 ± 1.10 (8948)

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. Summary of Baseline Characteristics (WATCHMAN FLX), continued

Characteristic	OPTION								
	Primary Analysis Intent-to-Treat (Combined Concomitant and Sequential Arms) (N=1600)			Concomitant Arm Subgroup (N=654)*			Sequential Arm Subgroup (N=946)†		
	WATCHMAN FLX	Control	P-value	WATCHMAN FLX (N=328)	Control (N=326)	P-value	WATCHMAN FLX (N=475)	Control (N=471)	P-value
CHADS ₂ Score (Continuous)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CHA ₂ DS ₂ -VASc Score (Continuous)	3.5±1.3 (803) (1.0, 8.0)	3.5±1.3 (797) (1.0, 8.0)	0.854	3.4±1.2 (328) (1.0, 8.0)	3.5±1.2 (326) (1.0, 7.0)	3.5±1.2 (326) (1.0, 7.0)	0.6804	3.6±1.3 (471) (1.0, 8.0)	0.9265
CHF	26.9% (216/803)	26.5% (211/797)	0.848	24.1% (79/328)	23.6% (77/326)	0.8889	28.8% (137/475)	28.5% (134/471)	0.8939
Hypertension	89.8% (721/803)	88.0% (701/797)	0.244	87.8% (288/328)	87.7% (286/326)	0.9767	91.2% (433/475)	88.1% (415/471)	0.1241
Age 65-74	54.5% (438/803)	54.5% (434/797)	0.971	51.5% (169/328)	53.4% (174/326)	0.6358	56.6% (269/475)	55.2% (260/471)	0.6578
Age ≥75	27.4% (220/803)	26.2% (209/797)	0.596	29.9% (98/328)	27.6% (90/326)	0.5212	25.7% (122/475)	25.3% (119/471)	0.8825
Diabetes	27.6% (222/803)	27.7% (221/797)	0.971	25.0% (82/328)	27.6% (90/326)	0.4489	29.5% (140/475)	27.8% (131/471)	0.5722
Previous stroke	10.3% (83/803)	12.5% (100/797)	0.165	9.1% (30/328)	12.3% (40/326)	0.1964	11.2% (53/475)	12.7% (60/471)	0.4535
Vascular disease	44.1% (354/803)	47.7% (380/797)	0.149	40.9% (134/328)	44.2% (144/326)	0.3908	46.3% (220/475)	50.1% (236/471)	0.2434
HAS-BLED Score (Continuous)	1.2±0.8 (803) (0.0, 4.0)	1.2±0.8 (797) (0.0, 5.0)	0.108	1.1±0.8 (328) (0.0, 4.0)	1.2±0.8 (326) (0.0, 5.0)	0.8889	1.2±0.9 (475) (0.0, 4.0)	1.2±0.8 (471) (0.0, 4.0)	0.1825

*defined as concomitant ablation and LAAC within 10 days of randomization in the WATCHMAN FLX arm and as ablation within 10 days of randomization in the control arm

†defined as ablation 90 to 180 days before LAAC in WATCHMAN FLX patients and as ablation occurring 90 to 180 days before randomization in control patients

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 9**.

Table 9. 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 11, Table 19, Table 27, and Table 32**.

** 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 58**) are not directly comparable to the results of the studies in **Table 9**.

ADVERSE EVENTS

Potential adverse events (in alphabetical order) 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 was safe and effective in subjects with non-valvular atrial fibrillation who were 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 CHADS₂ 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 CHADS₂ 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 10**.

Table 10. 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 CHADS₂ score was 2.2 ± 1.2, the mean CHA₂DS₂-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 CHADS₂ score was 2.3 ± 1.2, the mean CHA₂DS₂-VASc score was 3.5 ± 1.5, 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 5 and 7**.

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 11**. 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 11. 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		Rate Ratio (95% CrI) [*]
	Event Rate (per 100 Pt-yrs)	Event Rate/ Subject	Event Rate (per 100 Pt-yrs)	Event Rate/ Subject	
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**.

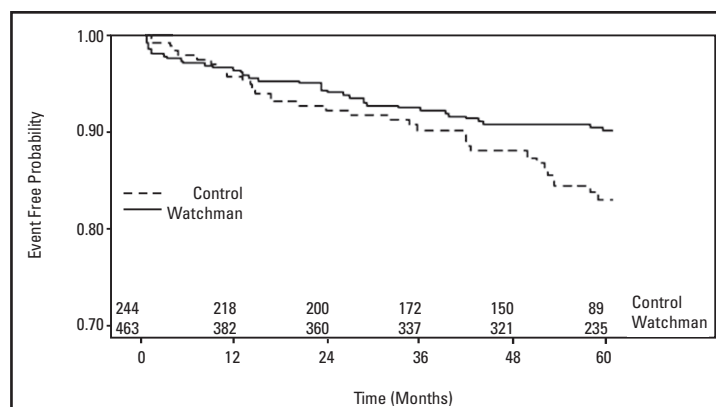


Figure 1. PROTECT AF Primary Effectiveness (2717 patient-years)

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 12**.

Table 12. 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 13**. 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 13. PROTECT AF Major Bleeding

Major Bleeding	WATCHMAN		Control	
	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 14**. Serious adverse events related to the WATCHMAN Device or implant procedure are shown in **Table 9**.

Table 14. 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 15.

Table 15. 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 were 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 CHADS₂ score of at least 2. Subjects with a CHADS₂ 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 CHADS₂ 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 CHADS₂ 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 16.

Table 16. 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 CHADS₂ score was 2.6 ± 1.0, the mean CHA₂DS₂-VASc score was 4.0 ± 1.1, the mean age was 74 years, 68% were male, and 94% were Caucasian. For subjects randomized to the Control group, the mean CHADS₂ score was 2.6 ± 1.0, the mean CHA₂DS₂-VASc score was 4.1 ± 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 5 and Table 7.

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 17).

Table 17. 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 18. The 18-month rate is the model-based probability of an event occurring within 18 months.

Table 18. 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.

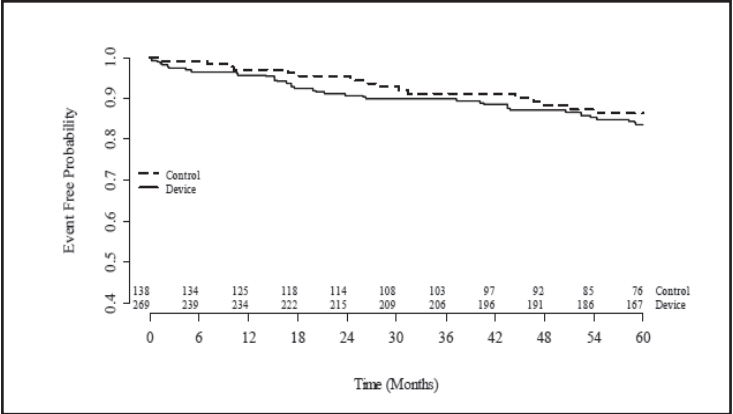


Figure 2. PREVAIL-Only Subjects – First Primary Endpoint Event

Table 19 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-yrs) favored the Control group, while the hemorrhagic stroke rate (0.2 vs. 0.5 per 100 pt-yrs) favored WATCHMAN, and death (cardiovascular or unexplained) rate (1.9 vs. 2.0 per 100 pt-yrs) was equivalent.

Table 19. PREVAIL Effectiveness Results and % of subjects who experienced 1 or more events – Final Dataset (PREVAIL-Only Subjects)

Randomization Allocation (2 Device: 1 Control)

Component of First Primary Endpoint	WATCHMAN		Control	
	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 (2.9%)
Stroke - Hemorrhagic	0.2 (2/1119)	2/269 (0.7%)	0.54 (3/554)	3/138 (2.2%)
Systemic Embolism	0.1 (1/1116)	1/269 (7.8%)	0 (0/557)	0/138 (0.0%)
Death (Cardiovascular or Unexplained)	1.9 (21/1119.5)	21/269 (7.8%)	1.9 (11/557)	11/138 (8.0%)
Ischemic Stroke and Systemic Embolism	1.8 (19/1070.5)	19/269 (7.0%)	1.3 (7/543.2)	4/138 (2.9%)
All stroke	1.9 (20/1073.9)	20/269 (7.4%)	0.7 (4/546.1)	7/138 (5.1%)

Second Primary Endpoint: Results of the Bayesian analysis for the second primary endpoint are shown in Table 20. The 18-month rate is the model-based probability of an event occurring within 18 months.

Table 20. 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.

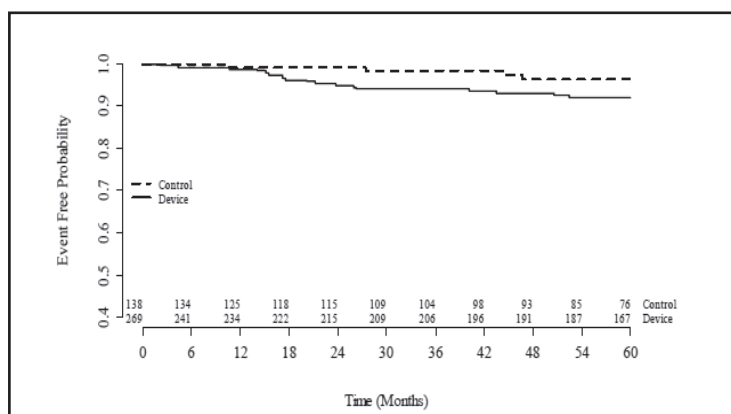


Figure 3. PREVAIL-Only Subjects – Second Primary Endpoint Event

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 21).

Table 21. 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 22.

Table 22. PREVAIL 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 23. 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 23. 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 – 6 months	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 24. Serious adverse events related to the WATCHMAN Device or implant procedure are shown in Table 9.

Table 24. PREVAIL-Only Serious Adverse Events

Event Type	WATCHMAN N=269				Control N=138			
	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	1.5	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 25.

Table 25. 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 were 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 CHADS₂ 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 CHADS₂ score was 2.5 ± 1.2, the mean CHA₂DS₂-VASC score was 3.9 ± 1.5, the mean age was 74 years, and 66% of subjects were male as shown in **Table 5** and **Table 7**.

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 26** and **27**. The primary safety rate was 3.1 events per 100-patient years.

Table 26. 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 27. 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 28**.

Table 28. 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 29**. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in **Table 9**.

Table 29. 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%

Event	Number of Events	Number of Subjects	% of Subjects N=566
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 30**.

Table 30. 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 were deemed by their physicians to be suitable for warfarin therapy.

Design: The CAP2 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 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 CHADS₂ score of at least 2. Subjects with a CHADS₂ 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 CHADS₂ score was 2.7 ± 1.1, the mean CHA₂DS₂-VASC score was 4.5 ± 1.3, the mean age was 75 years, and 61% of subjects were male as shown in **Table 5** and **Table 7**.

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 31. 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 32. 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 Tables 33 and 34.

Table 33. 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 34. 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 Tables 35 and 36.

Table 35. CAP2 Third Primary Endpoint

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

Table 36. 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 37. Serious adverse events related to the WATCHMAN Device or implant procedure are provided in Table 9.

Table 37. 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)	54	8.2% (47/576)
Rectal Bleeding	5	0.9% (5/576)
Cardiac Perforation	3	0.5% (3/576)
Myocardial Infarction	4	0.7% (4/576)
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	23	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 38.

Table 38. 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: 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) was 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). Follow-up visits in the LAAO Registry are required at 45 days, 6 months, 1 year and 2 years post-procedure. Two cohorts of 1,000 patients (primary and secondary) were included in the analysis. The Primary Cohort consisted of subjects who were eligible

for a WATCHMAN Device according to current U.S. indications with a calculated CHADS₂ score of ≥ 2 or a CHA₂DS₂-VASc score of ≥ 3 and excluded any patients who were 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 were complete, the next consecutive 1,000 patients implanted were included in the secondary cohort. Long-term outcomes (to 5 years) were assessed separately in Medicare Fee-for-Service (FFS) patients who received a WATCHMAN 2.5.

The pre-specified primary efficacy endpoints were analyzed only in the primary cohort and were 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 third primary endpoint, the primary safety endpoint, was calculated as the percent of all implanted or attempted patients who experienced 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 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. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications were excluded from this endpoint. Events related to subsequent WATCHMAN implant procedures were also excluded from this endpoint.

Demographics: A total of 1,000 subjects were enrolled in the primary cohort. The mean CHADS₂ score was 3.2 ± 1.2 , the mean CHA₂DS₂-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 Tables 5 and 7.

The NESTed SAP is complete.

Results: The WATCHMAN Device was successfully implanted in 947/992 (96%) subjects. Follow-up of the 1000 subjects was 1453.55 patient years.

First Primary Effectiveness Endpoint: The first primary endpoint event rate was 17.1% and the upper 1-sided 95% confidence bound of 20.0% exceeded the performance goal of 15% (Table 39).

Table 39. NESTed SAP First Primary Effectiveness Endpoint

	Time-to Event Rate*	Upper 1-sided 95% Confidence Bound	Performance Goal	P-value
Primary cohort	17.1%	20.0%	15.0%	0.94

*Rate of stroke (including ischemic and/or hemorrhagic), all-cause death and systemic embolism at 24 months

The first primary effectiveness endpoint events are shown in Table 40. The event rate was mainly driven by all-cause mortality (82.2% of primary endpoint events, two-thirds were non-cardiovascular deaths) as a result of a higher-than-expected baseline risk compared to the population used for setting the performance goal (CHA₂DS₂-VASc Score: NESTed SAP 5.0 ± 1.4 vs. eligible WATCHMAN subjects from PROTECT-AF, CAP, PREVAIL, and CAP2 4.3 ± 1.3).

Table 40. NESTed SAP First Primary Effectiveness Endpoint Events by Type of Event through 2 years

	NESTed SAP Primary Cohort N=1000		NESTed SAP Secondary Cohort N=965	
	% of Subjects	% of Endpoint	% of Subjects	% of Endpoint
All-cause Death, Hemorrhagic Stroke, Ischemic Stroke and Systemic Embolism	13.5% (135/1000)	100.0%	10.7% (103/965)	100.0%
All-cause Death	11.1% (111/1000)	82.2% (111/135)	8.7% (84/965)	81.6% (84/103)
Cardiovascular or non-specified Death	3.7% (37/1000)	27.4% (37/135)	2.4% (22/965)	22.3% (23/103)
Non-cardiovascular Death	7.4% (74/1000)	54.8% (74/135)	6.3% (61/965)	59.2% (61/103)
Hemorrhagic Stroke	0.5% (5/1000)	3.7% (5/135)	0.7% (7/965)	6.8% (7/103)
Ischemic Stroke	2.2% (22/1000)	16.3% (22/135)	1.8% (17/965)	16.5% (17/103)
Systemic Embolism	0.0% (0/1000)	0.0% (0/135)	0.1% (1/965)	1.0% (1/103)

Second Primary Effectiveness Endpoint: The second primary effectiveness endpoint event rate was 3.0% with an upper confidence bound of 4.6% which was below the prespecified performance goal of 7.0% (Table 41).

Table 41. NESTed SAP Second Primary Effectiveness Endpoint

	Time-to-Event Rate*	Upper 1-sided 95% Confidence Bound	Performance Goal	P-value
Primary cohort	3.0%	4.6%	7.0%	<0.001

*Rate of ischemic stroke or systemic embolism at 24 months

The second primary effectiveness endpoint events that occurred in NESTed SAP subjects are shown in Table 42.

Table 42. NESTed SAP Second Effectiveness Endpoint Events by Type of Event through 2 years

	NESTed SAP Primary Cohort N=1000		NESTed SAP Secondary Cohort N=965	
	% of Subjects	% of Endpoint	% of Subjects	% of Endpoint
Ischemic Stroke and Systemic Embolism	2.2% (22/1000)	100.0%	1.9% (18/965)	100.0%
Ischemic Stroke	2.2% (22/1000)	100.0% (22/22)	1.8% (17/965)	94.4% (17/18)
Systemic Embolism	0.0% (0/1000)	0.0% (0/22)	0.1% (1/965)	5.6% (1/18)

Primary Safety Endpoint: Fourteen subjects experienced a primary safety endpoint event between the 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 43 and Table 44.

Table 43: NESTed SAP Primary Safety Endpoint

N Subjects	% (n/N)	Upper 1-sided 95% Confidence Bound
1000	1.4% (14/1000)	2.18%

N = number, CI = confidence interval

The one-sided 95% confidence interval upper bound was 2.18%, which met the performance goal of 3.36% (p<0.0001). The primary safety endpoint events that occurred in 14 NESTed SAP Subjects are shown in Table 44.

Table 44. NESTed SAP Primary Safety Endpoint Events by Type of Event*

	NESTed SAP Primary Cohort N=1000		NESTed SAP Secondary Cohort N=965	
	N Events	% of Subjects	N Events	% of Subjects
Pericardial Effusion (requiring open cardiac surgery)	1	0.1%	2	0.2%
Death†	4	0.4%	1	0.1%
Ischemic Stroke	2	0.2%	3	0.3%
Surgery (unspecified)	5	0.5%	10	1.0%
Retroperitoneal Bleeding	3	0.3%	0	0.0%
Pseudoaneurysm (requiring surgical repair)	0	0.0%	2	0.2%
AV Fistula (requiring surgical repair)	0	0.0%	1	0.1%

*within 7 days of procedure or by hospital discharge

†The 4 deaths in the NESTed SAP primary cohort were adjudicated as follows: 2 pulmonary, 1 stroke, and 1 sudden cardiac death; the death in the secondary cohort was adjudicated as a stroke.

NESTed SAP long-term outcomes with WATCHMAN: As part of NESTed SAP, long-term (up to 5 years) outcomes with WATCHMAN were assessed in Medicare Fee-for-Service (FFS) subjects. The 100% Medicare FFS claims data Standard Analytical Files were the data source and the index inclusion period was April 1, 2016 to December 31, 2018. Subjects with at least 12 months of continuous FFS enrollment prior to the index date, who had a WATCHMAN implant during the index identification period and were ≥ 65 years of age were included in the analysis.

A total of 21,963 patients were analyzed. The mean CHA₂DS₂-VASc score was 4.34 ± 1.61 , the mean age was 76.9 ± 6.3 , and 57.8% were male. Time-to-event outcomes through 5 years are shown in Table 45.

Table 45. NESTed SAP Medicare FFS analysis: Outcomes after discharge through 5 years in patients implanted with WATCHMAN

Endpoint Event Type	Time-to-event Rate
First Primary Effectiveness Endpoint (all-cause death, ischemic stroke, hemorrhagic stroke, systemic embolism, or major bleeding)	44.89%
All-cause Death	36.77%
Ischemic Stroke	4.62%
Hemorrhagic Stroke	0.71%
Systemic Embolism	0.18%
Bleeding Event	11.85%
Second Primary Effectiveness (Ischemic stroke and Systemic Embolism)	4.77%
Major Bleeding	11.85%
Gastrointestinal Bleeding	10.29%
Intracranial Bleeding	0.97%
Other Bleeding event	0.76%

NESTed SAP Conclusions

NESTed SAP provides a valuable analysis of long-term outcomes in daily clinical practice in a large patient cohort. However, there are several limitations. This was a single-arm study with no comparator group. The NESTed SAP analysis extracted data from the NCDR LAO Registry which includes nearly all patients who were implanted with a WATCHMAN device. The Medicare FFS analysis excluded younger and potentially healthier patients and does not characterize medications. Despite the limitations of this analysis, the data

from this study demonstrated low rates of ischemic stroke and systemic embolism and suggests that during longer-term follow-up, WATCHMAN continues to be both safe and effective for the prevention of cardioembolic events for non-valvular atrial fibrillation patients.

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 CHA₂DS₂-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 CHA₂DS₂-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 **Tables 5 and 7** 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 46**.

Table 46. NESTed-DAPT 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 47**.

Table 47. NESTed-DAPT 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 48 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 48. NESTed-DAPT 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 49** presents the outcomes for the same two endpoints. **Table 50** presents a comparison of the components of the composite endpoint between the two cohorts

Table 49. NESTed-DAPT 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 50. NESTed-DAPT 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 CHA₂DS₂-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 6 and 8** above.

In the WATCHMAN FLX cohort, ischemic stroke occurred in 0.3% (4/1461) DAPT patients and 0.2% (3/1741) Control patients. **Tables 51 and 52** 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 51. NESTed-DAPT 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 52. NESTed-DAPT 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 was to establish the safety and effectiveness of the WATCHMAN FLX Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation who were eligible for non-vitamin K antagonist oral anticoagulation (NOAC) therapy to reduce the risk of stroke.

Design: PINNACLE FLX was 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 were 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 CHA₂DS₂-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 ≤ 5mm 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, and 21.9 months at the time of the final analysis. The 2-year follow-up visit occurred in 96.6% of the patients.

The PINNACLE FLX follow-up attendance is presented in Table 53.

Table 53. PINNACLE FLX 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 CHA₂DS₂-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 was the rate of effective LAA closure defined as any peri-device leak ≤ 5mm 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 54. At 45-day follow-up, 100% of subjects (389/389) exhibited adequate LAA closure. Table 55 reports the rate of effective LAA closure (peri-device leak ≤ 5mm demonstrated by TEE) at implant, 45-day and 12-month.

Table 54. PINNACLE FLX 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 55. PINNACLE FLX LAA Closure (per Core Laboratory assessment)

Peri-device Leak	Implant	45 Days	12 Months
Jet size 0 ≤ 5mm	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 ≤ 5mm	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 > 5mm	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*	2.6% (10/386) [1.2%, 4.7%]	0.8% (3/392) [0.2%, 2.2%]	1.1% (4/348) [0.3%, 2.9%]

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

*Site evaluation of TEEs assessed peri-device flow as < 5mm 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 56. Two ischemic stroke events occurred within 7 days of the implant procedure. The Secondary Effectiveness Endpoint was the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. Table 57 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 56. PINNACLE FLX 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 56. PINNACLE FLX 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 58.

Table 58. 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 58) are not directly comparable to the results of the studies in Table 9.

Table 59. PINNACLE FLX 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)

^aDocumented 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 60.

Table 60. 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 61.

Table 61. PINNACLE FLX 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 ^b	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.

^bCore 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 62.

Table 62. 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 was 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 was 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 CHA₂DS₂-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 was 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 implant, 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 CHA₂DS₂-VASc score was 4.0 ± 1.5, and the mean HAS-BLED score was 2.5 ± 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 63. The rates of effective closure of the LAA are shown post-procedure and at 45-days in Table 64. 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 at Table 65. 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 66. Medications used post-procedure through 45 days are reported in Table 67.

Table 63. 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 64. ICE-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%]
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 65. ICE-LAA 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 66. ICE-LAA 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 67. ICE-LAA 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

SURPASS DISCHARGE MEDICATION SUB-ANALYSIS

Primary Objective: The primary objective of the SURPASS discharge medication sub-analysis was to assess safety outcomes associated with the use of NOAC alone as an alternative to an OAC and aspirin as the post-implant medication regimen after LAA closure in a routine clinical setting.

Design: SURPASS will capture patients enrolled in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR). SURPASS data collection is on-going and began in August 2020 with the US commercial release of WATCHMAN FLX. The LAAO Registry is observational in nature. The data collected reflects the real-world setting and does not reflect a required clinical regimen. Discharge medication availability was the only inclusion criteria of the sub-analysis.

Key Safety Endpoint:

The occurrence of one of the following events between the time of the first implant procedure and within seven 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.

Additional Endpoints:

Additional analyses included the occurrence of the following endpoints at each LAAO Registry follow-up time points (discharge, 45 days, 6 months, and 12 months post-procedure):

- Death
- Stroke (Ischemic, Hemorrhagic)
- Systemic embolism
- Major bleeding

Enrollment: The SURPASS discharge medication sub-analysis data set includes all patients enrolled in the LAAO Registry who had a WATCHMAN FLX Device implant attempt and were discharged from Q3 2020 (05Aug2020) to Q3 2022 (30Sep2022).

Demographics: In the patients analyzed in the SURPASS sub-analysis, the mean CHA2DS2-VASc score was 4.8 ± 1.50 , the mean HAS-BLED score was 2.8 ± 1.1 , the mean age was 76.4 years, and 41% of patients were female.

Results: The composite rate of major adverse events was lowest in at 45 days (**Table 68**). The main driver of this composite event rate was major bleeding, which was lowest at 45 days in patients receiving NOAC alone (1.49%) or warfarin alone (1.37%) compared to patients receiving NOAC + aspirin (2.50%) and warfarin + aspirin (2.10%) and DAPT (2.83%). The rate of death was lowest in patients discharged on NOAC alone or NOAC + aspirin(**Table 68**).

At 6 months, the lowest rates of major adverse events were found in patients receiving NOAC alone or NOAC + aspirin at discharge; major bleeding was lowest in patients receiving NOAC alone or warfarin alone at discharge (**Table 69**). The rate of death was lowest in patients discharged on NOAC alone or NOAC + aspirin. Any stroke or TIA occurred at the lowest rates in the NOAC alone or warfarin alone groups; however, the rate of stroke and TIA was also very low in the NOAC + aspirin at discharge group (**Table 69**).

At 1 year, the lowest rates of major adverse events were found in patients discharged on NOAC alone and NOAC + aspirin; the rates of death were also lowest in these two groups (**Table 70**). The rate major bleeding continued to be lower in the NOAC alone and warfarin alone discharge medication groups.

After adjusting for differences in baseline characteristics, the use of NOAC alone compared with the NOAC + aspirin was associated with a significantly lower rate of major adverse events through 6 months and major bleeding between through 1 year of follow-up (**Table 71**). There were no statistically significant differences in the adjusted risk of death between the other discharge medication strategies through 1 year. The risk of stroke or TIA was increased in DAPT-treated patients through 6 months and in warfarin + aspirin treated patients at 1 year (**Table 71**). Overall rates of major adverse events were highest at all times points (45 days, 6 months and 1 year) in the DAPT group.

Table 68. Events Post Discharge to 45 days

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	2.46% (533)	3.40% (1514)	2.76% (59)	3.14% (192)	4.21% (358)
All death	0.55% (120)	0.59% (262)	1.26% (27)	0.73% (45)	0.93% (79)
Cardiovascular death/unknown cause death	0.28% (61)	0.27% (119)	0.66% (14)	0.34% (21)	0.48% (41)
Cardiovascular death	0.22% (47)	0.21% (92)	0.51% (11)	0.34% (21)	0.40% (34)
Death cause unknown/missing	0.06% (14)	0.06% (27)	0.14% (3)	0.00% (0)	0.08% (7)
Non-cardiovascular death	0.27% (59)	0.32% (143)	0.61% (13)	0.39% (24)	0.45% (38)
Pericardial effusion requiring surgical or percutaneous intervention	0.08% (18)	0.13% (59)	0.14% (3)	0.08% (5)	0.08% (7)
Ischemic stroke or systemic thromboembolism	0.20% (43)	0.14% (62)	0.14% (3)	0.16% (10)	0.27% (23)
Any stroke or TIA	0.34% (74)	0.28% (126)	0.37% (8)	0.33% (20)	0.50% (43)
All stroke	0.22% (48)	0.19% (86)	0.33% (7)	0.21% (13)	0.40% (34)
Ischemic stroke	0.20% (43)	0.13% (59)	0.14% (3)	0.15% (9)	0.26% (22)
Hemorrhagic stroke	0.02% (4)	0.05% (24)	0.19% (4)	0.07% (4)	0.13% (11)
Undetermined stroke	0.00% (1)	0.01% (4)	0.00% (0)	0.00% (0)	0.01% (1)
Transient ischemic attack	0.12% (26)	0.09% (41)	0.05% (1)	0.11% (7)	0.11% (9)
Systemic thromboembolism	0.00% (0)	0.01% (3)	0.00% (0)	0.02% (1)	0.01% (1)
Major bleeding	1.49% (322)	2.50% (1108)	1.37% (29)	2.10% (128)	2.83% (240)

Kaplan-Meier rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

Table 69. Events Post Discharge to 6 months

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	7.39% (1491)	8.10% (3465)	9.38% (184)	9.31% (551)	10.73% (870)
All death	3.23% (637)	3.14% (1319)	5.45% (106)	4.39% (257)	4.73% (376)
Cardiovascular death/unknown cause death	1.27% (250)	1.19% (497)	2.39% (46)	1.55% (90)	1.78% (140)
Cardiovascular death	1.01% (199)	0.92% (385)	1.71% (33)	1.23% (72)	1.50% (118)
Death cause unknown/missing	0.26% (51)	0.27% (112)	0.69% (13)	0.32% (18)	0.28% (22)
Non-cardiovascular death	1.98% (387)	1.97% (822)	3.14% (60)	2.88% (167)	3.00% (236)
Ischemic stroke or systemic thromboembolism	0.59% (117)	0.63% (260)	0.31% (6)	0.61% (35)	0.67% (53)
Pericardial effusion requiring surgical or percutaneous intervention	0.16% (32)	0.22% (94)	0.25% (5)	0.17% (10)	0.16% (13)
Ischemic stroke or systemic thromboembolism	0.59% (117)	0.63% (260)	0.31% (6)	0.61% (35)	0.67% (53)
Any stroke or TIA	0.95% (190)	0.99% (416)	0.88% (17)	1.23% (71)	1.21% (97)
All stroke	0.70% (140)	0.76% (317)	0.61% (12)	0.90% (52)	0.99% (79)
Ischemic stroke	0.53% (107)	0.59% (246)	0.31% (6)	0.55% (32)	0.60% (48)
Hemorrhagic stroke	0.15% (29)	0.15% (63)	0.30% (6)	0.29% (17)	0.34% (27)
Undetermined stroke	0.02% (4)	0.03% (14)	0.00% (0)	0.07% (4)	0.05% (4)
Transient ischemic attack	0.24% (50)	0.24% (102)	0.27% (5)	0.34% (20)	0.22% (18)
Systemic thromboembolism	0.05% (10)	0.04% (17)	0.00% (0)	0.05% (3)	0.08% (6)
Major bleeding	3.27% (664)	4.22% (1818)	3.73% (73)	4.34% (256)	5.22% (424)

Kaplan-Meier rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

Table 70. Events Post Discharge to 1 year

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	12.52% (2334)	12.66% (5127)	14.87% (275)	14.73% (833)	16.67% (1252)
All death	6.95% (1249)	6.33% (2483)	9.37% (171)	8.36% (464)	9.30% (669)
Cardiovascular death/unknown cause death	2.62% (464)	2.45% (944)	4.07% (73)	3.18% (172)	3.70% (258)
Cardiovascular death	2.07% (365)	1.85% (713)	3.14% (56)	2.48% (134)	3.08% (214)
Death cause unknown/missing	0.57% (99)	0.61% (231)	0.96% (17)	0.72% (38)	0.65% (44)
Non-cardiovascular death	4.44% (785)	3.98% (1539)	5.53% (98)	5.35% (292)	5.81% (411)
Pericardial effusion requiring surgical or percutaneous intervention	0.22% (42)	0.27% (112)	0.31% (6)	0.21% (12)	0.23% (17)
Ischemic stroke or systemic thromboembolism	1.22% (216)	1.28% (486)	0.94% (16)	1.34% (71)	1.16% (82)
Any stroke or TIA	1.82% (326)	1.87% (722)	1.81% (32)	2.11% (115)	2.04% (146)

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
All stroke	1.42% (253)	1.46% (560)	1.42% (25)	1.67% (90)	1.54% (112)
Ischemic stroke	1.14% (202)	1.18% (449)	0.94% (16)	1.22% (65)	1.04% (74)
Hemorrhagic stroke	0.25% (45)	0.25% (99)	0.48% (9)	0.37% (21)	0.42% (32)
Undetermined stroke	0.05% (9)	0.06% (22)	0.00% (0)	0.09% (5)	0.10% (7)
Transient ischemic attack	0.40% (74)	0.45% (174)	0.39% (7)	0.51% (28)	0.50% (34)
Systemic thromboembolism	0.09% (16)	0.11% (40)	0.00% (0)	0.12% (6)	0.15% (10)
Major bleeding	4.22% (816)	5.05% (2111)	4.59% (86)	5.34% (305)	6.34% (492)

Kaplan-Meier rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

Table 71. Adjusted Risk of Adverse Events in Mutually Exclusive Discharge Medication Groupings Compared With NOAC + Aspirin

	45 day		6 month		1 year	
	Univariate HR [95% CI]	Multivariate HR [95% CI]	Univariate HR [95% CI]	Multivariate HR [95% CI]	Univariate HR [95% CI]	Multivariate HR [95% CI]
Major adverse events						
NOAC alone	0.87 [0.80, 0.94]	0.80 [0.71, 0.90]	0.96 [0.90, 1.01]	0.92 [0.85, 0.99]	0.97 [0.92, 1.01]	0.96 [0.90, 1.02]
Warfarin + aspirin	1.07 [0.94, 1.22]	0.85 [0.72, 1.01]	1.20 [1.11, 1.31]	0.99 [0.88, 1.11]	1.17 [1.09, 1.25]	1.00 [0.91, 1.10]
Warfarin alone	0.91 [0.73, 1.14]	0.78 [0.60, 1.02]	1.16 [1.01, 1.34]	0.92 [0.78, 1.10]	1.16 [1.04, 1.31]	0.99 [0.86, 1.15]
DAPT	1.47 [1.33, 1.62]	0.94 [0.81, 1.10]	1.44 [1.35, 1.55]	0.93 [0.84, 1.04]	1.28 [1.21, 1.36]	0.94 [0.86, 1.03]
Death						
NOAC alone	0.94 [0.76, 1.17]	0.93 [0.71, 1.22]	1.03 [0.93, 1.13]	1.00 [0.88, 1.13]	1.01 [0.95, 1.08]	1.02 [0.93, 1.12]
Warfarin + aspirin	1.25 [0.91, 1.71]	0.92 [0.61, 1.41]	1.41 [1.23, 1.61]	1.06 [0.89, 1.26]	1.23 [1.11, 1.36]	1.06 [0.94, 1.21]
Warfarin alone	2.15 [1.45, 3.20]	1.61 [0.98, 2.63]	1.77 [1.45, 2.15]	1.22 [0.95, 1.56]	1.51 [1.29, 1.76]	1.24 [1.02, 1.51]
DAPT	1.58 [1.23, 2.03]	0.84 [0.58, 1.23]	1.52 [1.36, 1.71]	0.95 [0.80, 1.13]	1.21 [1.11, 1.32]	1.00 [0.88, 1.14]
Stroke or TIA						
NOAC alone	1.10 [0.85, 1.42]	1.10 [0.85, 1.43]	0.95 [0.81, 1.12]	0.97 [0.82, 1.15]	0.98 [0.86, 1.11]	1.04 [0.88, 1.24]
Warfarin + aspirin	1.04 [0.68, 1.60]	1.08 [0.70, 1.66]	1.19 [0.93, 1.52]	1.17 [0.91, 1.50]	1.29 [1.06, 1.56]	1.31 [1.04, 1.65]
Warfarin alone	1.11 [0.57, 2.17]	1.16 [0.59, 2.26]	0.85 [0.53, 1.36]	0.91 [0.57, 1.46]	1.21 [0.85, 1.71]	1.45 [0.99, 2.11]
DAPT	1.77 [1.31, 2.39]	1.80 [1.33, 2.44]	1.29 [1.05, 1.59]	1.25 [1.01, 1.54]	1.13 [0.95, 1.34]	1.27 [0.99, 1.64]
Major Bleeding						
NOAC alone	0.79 [0.72, 0.88]	0.73 [0.64, 0.84]	0.87 [0.80, 0.94]	0.82 [0.73, 0.91]	0.89 [0.83, 0.96]	0.84 [0.76, 0.93]
Warfarin + aspirin	1.05 [0.91, 1.23]	0.92 [0.76, 1.11]	1.14 [1.01, 1.28]	0.97 [0.83, 1.14]	1.10 [0.99, 1.23]	0.95 [0.82, 1.11]
Warfarin alone	0.72 [0.54, 0.96]	0.62 [0.44, 0.87]	0.93 [0.75, 1.14]	0.72 [0.55, 0.93]	0.90 [0.74, 1.09]	0.78 [0.61, 0.99]
DAPT	1.45 [1.30, 1.63]	0.84 [0.70, 1.00]	1.43 [1.30, 1.57]	0.81 [0.69, 0.94]	1.38 [1.26, 1.51]	0.81 [0.70, 0.93]

Reference NOAC + aspirin

HR=hazard ratio

To adjust for differences in baseline characteristics, multivariable Cox regression was performed using NOAC plus aspirin as the reference group. Variables were included in the regression analysis if they had a P value <0.05 in univariate analysis or were clinically known to be associated with the study outcomes. The final variables included in the analysis included age, sex, race, CHA2DS2-VASc score components (congestive heart failure, left ventricular dysfunction, hypertension, diabetes mellitus, transient ischemic). The confidence intervals are exploratory in nature and should not be used in place of hypothesis testing.

Conclusions:

Patients discharged on NOAC alone had lower rates of major adverse events than NOAC + aspirin or warfarin + aspirin at 45 days and 6 months post discharge. Fewer major bleeding events occurred in the NOAC alone and warfarin alone groups after adjustment for differences in baseline characteristics.

OPTION

Primary Objective: The primary objective of this study was to determine if LAAC with the WATCHMAN FLX device was a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high-risk patients with NVAF.

Design: OPTION was a prospective, randomized, multicenter, global investigation. Eligible patients in each arm received a catheter ablation procedure for NVAF.

Patients were randomized to OAC (Control) or WATCHMAN FLX in equal proportion (1:1 Control:WATCHMAN FLX). Catheter ablation occurred prior to LAAC in the WATCHMAN FLX cohort. The ablation could have occurred sequential to the LAAC (90 to 180 days prior to randomization). Alternatively, the catheter ablation procedure could have occurred concomitantly, at the time or within 10 days of the subsequent WATCHMAN FLX implantation. In this concomitant cohort, if procedures were done at the same time, the ablation immediately preceded the LAAC procedure. Randomization was stratified by sequential vs. concomitant catheter ablation ± WATCHMAN FLX implantation to help ensure balance of treatment assignments within the sequential and concomitant groups. The planned ablation procedure type, concomitant or sequential, must have been specified prior to randomizing the subject. While subjects were randomized to device and control groups, subjects were not randomized to sequential or concomitant subgroups. The OPTION IDE was not statistically powered nor designed for a direct comparison between concomitant and sequential cohorts.

Key Inclusion/Exclusion Criteria: Patients were required to have a calculated CHA2DS2-VASc score of ≥2 for males or ≥3 for females and be deemed suitable for OAC as per current guidelines at time of enrollment. Exclusion criteria included the need for long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, recent stroke or transient ischemic attack, recent major bleeding event, history of atrial septal repair or presence of a patent foramen ovale/atrial septal defect device, implanted mechanical valve, life expectancy of less than two years, left ventricular ejection fraction <30%, existing pericardial effusion >5mm, high-risk patent foramen ovale, or significant mitral valve stenosis.

The study had the following primary and secondary endpoints:

- Primary safety endpoint: Non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) through 36 months
- Primary effectiveness endpoint: Stroke (including ischemic and/or hemorrhagic), all-cause death, and systemic embolism at 36 months
- Secondary endpoint: ISTH major bleeding (including procedural bleeding) at 36 months

OPTION was designed to test the hypotheses that LAAC would be superior to oral anticoagulation with respect to the primary safety end point and noninferior with respect to the primary efficacy end point in catheter ablation patients. The primary analysis population was the intent-to-treat population with each patient analyzed as being part of their randomized group regardless of the actual treatment received.

A sample of 1280 patients was estimated to provide the trial with 86% power to show superiority of LAAC versus oral anticoagulation with regard to the primary safety end point assuming a rate of 14% in the LAAC

group and 20% in the OAC group. A sample size of 1600 patients was chosen to allow for withdrawals and loss to follow-up. Testing for superiority at a two-sided alpha level of 0.05 was performed with a log rank P value based on the Kaplan-Meier estimation.

The trial was also powered to detect noninferiority with respect to the primary efficacy end point. It was assumed that 10% of the patients in each group would have a primary efficacy event. A noninferiority margin of 5 percentage points was chosen, which represents a relative risk of 1.5. With 1600 patients, the trial provides more than 85% power to show noninferiority on the basis of the Farrington-Manning test at a one-sided type I error of 0.025. The study was considered successful if superiority testing of the primary safety end point and noninferiority testing of the primary efficacy end point were met.

If study success was met, a secondary end point, ISTH major bleeding at 36 months, would be tested for non-inferiority. With an assumed 11% rate in each cohort of patients and noninferiority margin of 5.25 percentage points, 1600 patients provided 84% power to show noninferiority on the basis of the Farrington-Manning test at a one-sided type I error of 0.025. If the non-inferiority hypothesis objective was met, a superiority test would subsequently be performed as part of hierarchical testing and a one-sided p-value of 0.025 will be considered significant.

To avoid multiplicity issues for additional statistical tests, a hierarchical order for the hypothesis tests and a testing significance level of a one-sided alpha of 0.025 for all hypotheses was used. The hypothesis testing followed the order below.

1. Superiority testing of the primary safety end point and non-inferiority testing of the primary efficacy end point,
2. Non-inferiority testing of the secondary end point,
3. Superiority testing of the secondary end point, and
4. Superiority testing of the primary efficacy end point.

Enrollment: Between June 11, 2019 and June 28, 2021, at 106 investigational sites, 803 patients were assigned to device implant and 797 to anticoagulation. Fifty patients in the device group did not receive a device and continued anticoagulation. One anticoagulation patient received a device in error. A total of 82 patients in the anticoagulation group crossed over to the device group; 67 of these patients (82%) did so after a primary end-point event occurred. In the overall study, the mean (±SD) age of patients was 69.6 ±7.7 years and 34.1% were women. The mean CHA₂DS₂-VASc score was 3.5±1.3, and the mean HAS-BLED score was 1.2±0.8.

The concomitant cohort was defined in the WATCHMAN FLX arm as concomitant ablation and LAAC within 10 days of randomization (n=326; 40.9% of WATCHMAN FLX patients). In the control arm, the concomitant cohort was defined as ablation within 10 days of randomization (n=326; 40.8% of control patients). The sequential cohort was defined in the WATCHMAN FLX arm as ablation 90 to 180 days before LAAC (n=475, 59.1% of WATCHMAN FLX patients). In the control arm, the sequential cohort was defined as ablation occurring 90 to 180 days before randomization (n=475, 59.2% of control patients).

Subject Demographics and Baseline Clinical Features: For patients randomized to the WATCHMAN FLX group, the mean CHA₂DS₂-VASc score was 3.5 ± 1.3, the mean age was 70 years, 35% were female, and 84% were Caucasian. For patients randomized to the Control group, the mean CHA₂DS₂-VASc score was 3.5 ± 1.3, the mean age was 70 years, 33% were female, and 86% were Caucasian. The two treatment groups had no statistically significant differences in baseline demographic and clinical characteristics as shown in **Table 6** and **Table 8**.

In the concomitant subgroup, the mean CHA₂DS₂-VASc score was 3.4 ± 1.2, the mean age was 70 years, 37% were female, and 78% were Caucasian in patients randomized to the WATCHMAN FLX arm. The mean CHA₂DS₂-VASc score was 3.5 ± 1.2, the mean age was 70 years, 32% were female, and 80% were Caucasian in patients randomized to the Control arm.

In the sequential subgroup, the mean CHA₂DS₂-VASc score was 3.6 ± 1.3, the mean age was 69 years, 34% were female, and 88% were Caucasian in patients randomized to the WATCHMAN FLX arm. For patients randomized to the Control group, the mean CHA₂DS₂-VASc score was 3.6 ± 1.3, the mean age was 69 years, 34% were female, and 90% were Caucasian.

Results: In the WATCHMAN FLX group, implantation was successful in 98.8% of patients; device or procedure-related complications occurred in 22 patients assigned to the device group and one patient in the anticoagulation group that crossed over to receive a device. Device success was 99.1% in concomitant WATCHMAN FLX patients and 98.7% in sequential WATCHMAN FLX patients.

Table 72 displays findings from LAA imaging at procedure, 90 days, and 1 year for patients randomized to WATCHMAN FLX overall and in the concomitant and sequential ablation timing subgroups.

Complete seal at 3 months occurred in 77.0% of concomitant subgroup (patients who received WATCHMAN FLX patients at the same time as catheter ablation). In the sequential subgroup (patients who received ablation at least 90 days prior to WATCHMAN FLX implant), 83.9% of patients had complete seal at 3 months. In the concomitant subgroup, complete device seal was observed in 78.6% of subjects at 12 months. In the sequential group, complete seal was identified in 80.3% of subjects at 12 months. The 12-month rate of device-related thrombus was 1.9% (**Table 72**). Three patients with leak >0 mm to ≤3 mm at 12 months had a stroke later in follow-up; 2 were from the sequential subgroup (ischemic stroke occurred at 977 and 1101 days post procedure) and 1 from the concomitant subgroup (ischemic stroke occurred at 1023 days post LAAC procedure).

The core lab adjudicated DRT in 3 patients in the concomitant ablation group (1.0%) and 5 patients in the sequential subgroup (1.2%) at 3-months. At 12-months, the core lab adjudicated DRT in 10 patients in the concomitant subgroup (3.5%) and 3 patients in the sequential subgroup (0.7%). Most DRT were characterized as non-mobile laminar in either subgroup. No patients in either ablation timing group who had a DRT at 3 or 12 months experienced a stroke or systemic embolism during follow-up.

Table 72. Core Laboratory Adjudicated Transesophageal Echocardiogram Characteristics in Ablation + WATCHMAN FLX Patients

	Procedure	90 Days	1 year
All Randomized Patients			
LAA seal			
Residual leak — no. (%)			
Complete seal (0mm)	97.2% (650/669)	81.0% (572/706)	79.7% (529/664)
>0mm to ≤3mm	2.7% (18/669)	17.6% (124/706)	18.1% (120/664)

	Procedure	90 Days	1 year
All Randomized Patients			
>3mm to ≤5mm	0.0% (0/669)	1.1% (8/706)	2.1% (14/664)
>5mm	0.1% (1/669)	0.3% (2/706)	0.2% (1/664)
Residual flow not assessed	0.0% (0/669)	0.6% (4/710)	0.7% (5/669)
Device-related thrombus — no. (%)	NA	1.1% (8/734)	1.9% (13/702)
Laminar	NA	0.4% (3/734)	1.3% (9/702)
Mobile	NA	0.0% (0/734)	0.3% (2/702)
Non-mobile	NA	0.4% (3/734)	0.9% (6/702)
Pedunculated	NA	0.5% (4/734)	0.4% (3/702)
Mobile	NA	0.4% (3/734)	0.4% (3/702)
Non-mobile	NA	0.0% (0/734)	0.0% (0/702)
Concomitant Patients*			
LAA seal			
Residual leak — no. (%)			
Complete seal (0mm)	97.3% (255/262)	77.0% (224/291)	78.6% (206/262)
>0mm to ≤3mm	2.7% (7/262)	22.0% (64/291)	18.7% (49/262)
>3mm to ≤5mm	0.0% (0/262)	1.0% (3/291)	2.3% (6/262)
>5mm	0.0% (0/262)	0.0% (0/291)	0.4% (1/262)
Residual flow not assessed	0.0% (0/262)	0.7% (2/293)	1.5% (4/266)
Device-related thrombus — no. (%)	N/A	1.0% (3/304)	3.5% (10/282)
Laminar	N/A	0.3% (1/304)	2.8% (8/282)
Mobile	N/A	0.0% (0/304)	0.7% (2/282)
Non-mobile	N/A	0.3% (1/304)	1.8% (5/282)
Pedunculated	N/A	0.7% (2/304)	0.4% (1/282)
Mobile	N/A	0.3% (1/304)	0.4% (1/282)
Non-mobile	N/A	0.0% (0/304)	0.0% (0/282)
Sequential Patients†			
LAA seal			
Residual leak — no. (%)			
Complete seal (0mm)	97.1% (395/407)	83.9% (348/415)	80.3% (323/402)
>0mm to ≤3mm	2.7% (11/407)	14.5% (60/415)	17.7% (71/402)
>3mm to ≤5mm	0.0% (0/407)	1.2% (5/415)	2.0% (8/402)
>5mm	0.2% (1/407)	0.5% (2/415)	0.0% (0/402)
Residual flow not assessed	0.0% (0/407)	0.5% (2/417)	0.2% (1/403)
Device-related thrombus — no. (%)	N/A	1.2% (5/430)	0.7% (3/420)
Laminar	N/A	0.5% (2/430)	0.2% (1/420)
Mobile	N/A	0.0% (0/430)	0.0% (0/420)
Non-mobile	N/A	0.5% (2/430)	0.2% (1/420)
Pedunculated	N/A	0.5% (2/430)	0.5% (2/420)
Mobile	N/A	0.5% (2/430)	0.5% (2/420)
Non-mobile	N/A	0.0% (0/430)	0.0% (0/420)

Core laboratory adjudicated; N/A indicates not assessed
*defined as concomitant ablation and LAAC within 10 days of randomization in the WATCHMAN FLX arm and as ablation within 10 days of randomization in the control arm
†defined as ablation 90 to 180 days before LAAC in WATCHMAN FLX patients and as ablation occurring 90 to 180 days before randomization in control patients

Primary and Secondary Endpoints

The primary safety outcome occurred in 8.5% of WATCHMAN FLX patients and 18.1% control patients (hazard ratio, 0.44; 95% CI, 0.33 to 0.59; device superiority against control was achieved for the primary safety endpoint (p-value <0.0001; **Table 73, Figure 4, Table 74**).

The primary efficacy outcome occurred in 5.3% of patients assigned to WATCHMAN FLX and 5.8% assigned to control (hazard ratio, 0.91; 95% CI, 0.59 to 1.39; difference, -0.5%; 1-sided 97.5% Z upper confidence bound, 1.8%, noninferiority margin 5%. Thus, device noninferiority against control was achieved for the primary effectiveness endpoint (p-value <0.0001; **Table 73, Figure 4**).

The secondary end point of ISTH major bleeding (including procedural bleeding) occurred in 3.9% of WATCHMAN FLX patients and 5.0% of control (difference, -1.1%; 1-sided 97.5% Z upper confidence bound 1.0%, noninferiority margin 5.25%; hazard ratio, 0.77; 95% CI, 0.48 to 1.24) and met the criteria for noninferiority (P <0.0001) but not superiority (P=0.28; **Table 73, Figure 4**).

Table 73. OPTION Primary and Secondary Endpoints (Intent-to-treat)

End Point	WATCHMAN FLX (N=803)	Control (N=797)	Difference (1-sided 97.5% Z upper confidence bound)	Non inferiority Margin	P Value
Primary Safety End point†					Superiority
Non-procedural ISTH major or clinically-relevant non-major bleeding - % (number of subjects)	8.5% (65)	18.1% (137)	=	=	<0.0001
Primary Efficacy End point‡					Noninferiority
Composite of all-cause death, stroke, or systemic embolism - % (number of subjects)	5.3% (41)	5.8% (44)	-0.5% (1.8%)	5.0%	<0.0001
Secondary¶					Noninferiority
ISTH Major bleeding - % (number of subjects)	3.9% (30)	5.0% (38)	-1.1% (1.0%)	5.25%	<0.0001

*All analyses were performed in the intention-to-treat population (all patients who underwent randomization, grouped according to their assigned treatment; the start time of follow-up for the intent-to-treat analysis was the day of randomization). Testing was performed in the following steps with each step needing to reject the null hypothesis in order to proceed to the next step: 1) superiority testing of the primary safety end point and noninferiority testing of the primary efficacy end point, 2) noninferiority testing of the secondary end point, 3) superiority testing of the secondary end point, and 4) superiority testing of the primary efficacy end point. The study was considered successful if superiority testing of the primary safety end point and noninferiority testing of the primary efficacy end point were both met.

†Composite of non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant nonmajor bleeding), non-procedural events are those occurring after 3 days post procedure in the device arm. P Value is from the Log-Rank test and is based on the Kaplan-Meier estimation for the superiority testing.

‡Composite of non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant nonmajor bleeding), non-procedural events are those occurring after 3 days post procedure in the device arm. Event rates are based on the Kaplan-Meier estimates. P Value is based on the Log-Rank test for superiority testing.

§Composite of stroke, all-cause death, or systemic embolism 36 months post randomization. Event rates are based on the Kaplan-Meier estimates. P Value is from the test of non-inferiority for the Kaplan-Meier event rates and using a Corn-Nougue approach to estimate the Z-statistic with Greenwood formula for estimating the variance.

¶The secondary end point was ISTH major bleeding through 36 months after randomization (including procedural bleeding). Event rates are the Kaplan-Meier estimates. P Value is from the test of non-inferiority for the Kaplan-Meier event rates and using a Corn-Nougue approach to estimate the Z-statistic with Greenwood formula for estimating the variance.

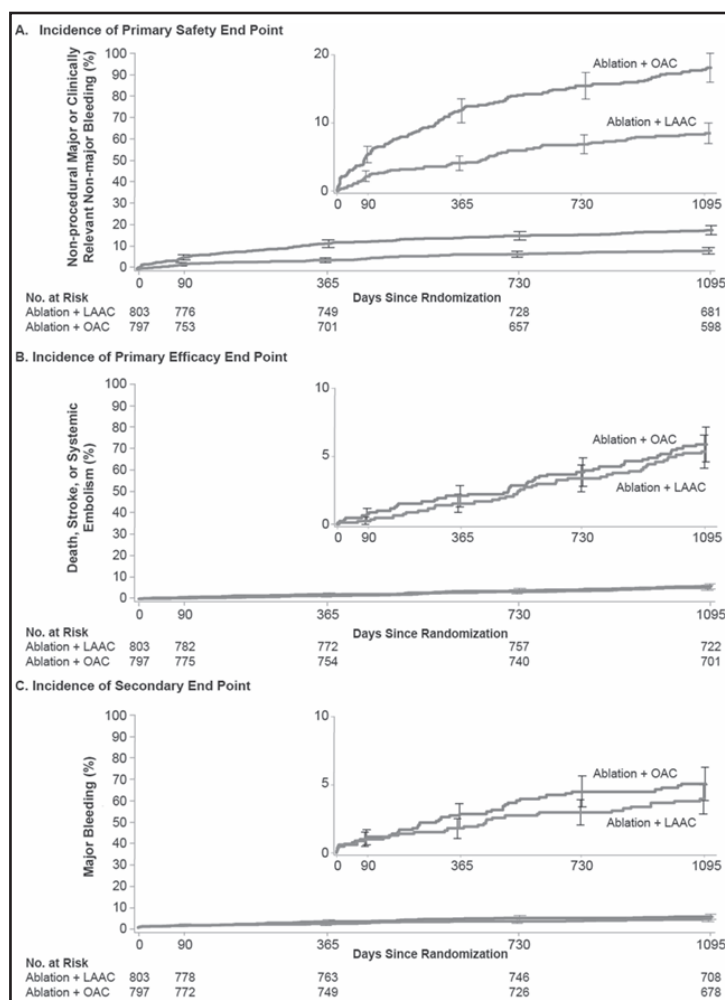


Figure 4. Primary and Secondary End Points

Shown in Panel A are the Kaplan-Meier survival curves for the primary safety end point of non-procedural bleeding through 36 months after randomization based on the International Society on Thrombosis and Haemostasis [ISTH] major bleeding or clinically relevant nonmajor bleeding definitions. Panel B shows the primary efficacy end point of all-cause death, stroke, or systemic embolism 36 months post randomization. Panel C shows the Kaplan-Meier survival curves for the secondary end point of major bleeding through 36 months (including procedural bleeding) after randomization based on the International Society on Thrombosis and Haemostasis [ISTH] major bleeding. Shown are the two primary cohorts, patients who underwent catheter ablation and implantation of a left atrial appendage closure device (blue) and those who underwent catheter ablation only (orange).

Additional clinical end points through 3 years are shown in Table 74. All-cause mortality occurred in 3.8% and 4.5% patients and ischemic stroke occurred in 1.2% and 1.3% of patients in the device and anticoagulation groups, respectively. Hemorrhagic stroke occurred in 0.4% of patients in both groups. Systemic embolism occurred in 0.3% of device and 0.1% of anticoagulation patients. Pericardial effusion requiring intervention occurred in 0.3% of device patients compared to 0.7% anticoagulation patients.

Table 74. Additional Clinical End Points at 36 months*

	WATCHMAN FLX (N=803)	Control (N=797)
All-cause mortality	29 (3.8)	34 (4.5)
Cardiovascular/unexplained	15 (2.0)	15 (2.0)
Cardiovascular	9 (1.2)	10 (1.3)
Unexplained	6 (0.8)	5 (0.7)
Non-cardiovascular	14 (1.9)	19 (2.6)
Stroke or systemic embolism	14 (1.8)	16 (2.1)
Ischemic stroke or systemic embolism	11 (1.5)	11 (1.5)
Stroke	12 (1.6)	15 (2.0)
Ischemic	9 (1.2)	10 (1.3)
Hemorrhagic	3 (0.4)	3 (0.4)
Systemic embolism	2 (0.3)	1 (0.1)
Transient ischemic attack	12 (1.6)	11 (1.5)
ISTH bleeding	73 (9.5)	137 (18.1)
Major bleeding	30 (3.9)	38 (5.0)
Clinically relevant nonmajor bleeding	46 (6.0)	110 (14.6)
Pericardial effusion resulting in an intervention	2 (0.3)	5 (0.7)
Site-reported device related SAE	15 (1.9)	--
Site-reported procedure related SAE	29 (3.7)	--

Kaplan-Meier rates ; Numbers are number of events (%). CEC=adjudicated events. SAE=serious adverse events
No significant interaction was found between ablation group and treatment arm (Table 75).

Table 75. OPTION Primary and Secondary Endpoints (Intent-to-treat) in the Concomitant and Sequential Subgroups

	WATCHMAN FLX (N=803)	Control (N=797)	Hazard Ratio [95% C.I.]	P value	Interaction P value
Primary Safety Endpoint ^a					
Sequential	(N=475)	(N=471)			0.2411
	8.8% (40)	21.5% (95)	0.38 [0.27, 0.56]	<.0001	
Concomitant	(N=328)	(N=326)			
	8.0% (25)	13.3% (42)	0.56 [0.34, 0.92]	0.0200	
Primary Effectiveness Endpoint ^b					
Sequential	(N=475)	(N=471)			0.5393
	4.2% (19)	5.3% (23)	0.79 [0.43, 1.45]	0.4490	
Concomitant	(N=328)	(N=326)			
	7.0% (22)	6.7% (21)	1.04 [0.57, 1.88]	0.9083	
Secondary Endpoint ^c					
Sequential	(N=475)	(N=471)			0.1055
	3.1% (14)	5.7% (25)	0.54 [0.28, 1.04]	0.0608	
Concomitant	(N=328)	(N=326)			
	5.1% (16)	4.1% (13)	1.22 [0.59, 2.53]	0.5965	

Kaplan-Meier rates presented as % (number of events)
a: Composite of non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant non-major bleeding), non-procedural events are those occurring after 3 days post procedure.
b: Composite of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism through 36 months.
c: ISTH major bleeding through 36 months (including procedural bleeding).
P-value from Cox regression

Table 76 shows mortality, stroke, and bleeding rates in sequential and concomitant patients at 36 months post randomization. The rate of clinically relevant non-major bleeding was noticeably lower in the WATCHMAN FLX group compared to Control for both sequential and concomitant patients.

Table 76. Additional Clinical End Points at 36 months*

	WATCHMAN FLX	Control	P-value
Concomitant*			
All-cause mortality	5.4% (17)	5.4% (17)	0.9776
Cardiovascular/unexplained	3.2% (10)	1.9% (6)	0.3305
Cardiovascular	2.5% (8)	1.3% (4)	0.2590
Unexplained	0.6% (2)	0.7% (2)	0.9930
Non-cardiovascular	2.3% (7)	3.6% (11)	0.3390
Stroke or systemic embolism	2.3% (7)	2.9% (9)	0.6013
Ischemic stroke or systemic embolism	1.6% (5)	1.9% (6)	0.7476
Stroke	2.3% (7)	2.5% (8)	0.7784
Ischemic	1.6% (5)	1.6% (5)	0.9835
Hemorrhagic	0.6% (2)	0.3% (1)	0.5710
Systemic embolism	0.0% (0)	0.3% (1)	0.3173
Transient ischemic attack	1.6% (5)	1.3% (4)	0.7448
ISTH bleeding	9.2% (29)	13.3% (42)	0.0823
Major bleeding	5.1% (16)	4.1% (13)	0.5965
Clinically relevant nonmajor bleeding	4.4% (14)	10.8% (34)	0.0021
Pericardial effusion resulting in an intervention	0.3% (1)	0.9% (3)	0.3105
Site-reported device related SAE	2.5% (8)	--	
Site-reported procedure related SAE	5.5% (18)	--	
Sequential†			
All-cause mortality	2.7% (12)	3.9% (17)	0.2921
Cardiovascular/unexplained	1.1% (5)	2.1% (9)	0.2465
Cardiovascular	0.2% (1)	1.4% (6)	0.0518
Unexplained	0.9% (4)	0.7% (3)	0.7595
Non-cardiovascular	1.6% (7)	1.9% (8)	0.7298
Stroke or systemic embolism	1.6% (7)	1.6% (7)	0.9530
Ischemic stroke or systemic embolism	1.3% (6)	1.1% (5)	0.8105
Stroke	1.1% (5)	1.6% (7)	0.5266
Ischemic	0.9% (4)	1.1% (5)	0.6949
Hemorrhagic	0.2% (1)	0.4% (2)	0.5573
Systemic embolism	0.4% (2)	0.0% (0)	0.1650
Transient ischemic attack	1.6% (7)	1.6% (7)	0.9428
ISTH bleeding	9.7% (44)	21.5% (95)	<.0001
Major bleeding	3.1% (14)	5.7% (25)	0.0608
Clinically relevant nonmajor bleeding	7.0% (32)	17.3% (76)	<.0001
Pericardial effusion resulting in an intervention	0.2% (1)	0.5% (2)	0.5350
Site-reported device related SAE	1.5% (7)	--	
Site-reported procedure related SAE	2.4% (11)	--	

Kaplan-Meier rates presented as % (number of events). CEC=adjudicated events. SAE=serious adverse event. Ablation-related SAEs in the sequential cohort were not collected in the OPTION study. None of the procedure-related SAEs led to death.

Use of antiplatelet and anticoagulant medication throughout follow-up is shown in Table 77.
After implantation, WATCHMAN FLX patients were prescribed market-approved OAC and aspirin (75-100mg recommended) until the 3-month visit followed by aspirin until at least the 12-month visit. Aspirin was recommended for duration of the trial (3 years). The most common reason for resuming oral anticoagulation in the WATCHMAN FLX arm was cardiac ablation or cardioversion.
Control patients continued or started market-approved OAC use per IFU for atrial fibrillation stroke prevention post catheter ablation and were required to remain on OAC for the duration of the trial (3 years).

Table 77. Antiplatelet/Anticoagulant Medications, Intention-to-Treat Analysis Set

	WATCHMAN FLX	Control
3-month follow-up visit		
SAPT	7.1% (55/772)	0.1% (1/754)
DAPT	2.1% (16/772)	0.1% (1/754)
Aspirin and Warfarin	3.4% (26/772)	1.6% (12/754)
Aspirin and DOAC	80.7% (623/772)	20.3% (153/754)
Warfarin alone	0.5% (4/772)	3.8% (29/754)
DOAC alone	5.8% (45/772)	72.7% (548/754)
Other medication regimen	0.1% (1/772)	0.0% (0/754)
None	0.4% (3/772)	1.3% (10/754)
1-year follow-up visit		
SAPT	81.9% (615/751)	4.9% (35/714)
DAPT	4.1% (31/751)	1.0% (7/714)
Aspirin and Warfarin	0.3% (2/751)	1.3% (9/714)
Aspirin and DOAC	5.6% (42/751)	16.8% (120/714)
Warfarin alone	0.7% (5/751)	3.2% (23/714)
DOAC alone	4.5% (34/751)	71.3% (509/714)
Other medication regimen	0.3% (2/751)	0.1% (1/714)
None	2.7% (20/751)	1.4% (10/714)
2-year follow-up visit		
SAPT	76.9% (567/737)	7.6% (53/698)
DAPT	4.3% (32/737)	1.3% (9/698)
Aspirin and Warfarin	0.0% (0/737)	1.1% (8/698)
Aspirin and DOAC	3.5% (26/737)	15.9% (111/698)
Warfarin alone	0.7% (5/737)	3.4% (24/698)
DOAC alone	5.3% (39/737)	67.6% (472/698)
Other medication regimen	0.3% (2/737)	0.1% (1/698)
None	9.0% (66/737)	2.9% (20/698)
3-year follow-up visit		
SAPT	77.5% (553/714)	9.9% (67/679)
DAPT	3.8% (27/714)	1.2% (8/679)
Aspirin and Warfarin	0.1% (1/714)	1.0% (7/679)
Aspirin and DOAC	3.5% (25/714)	13.8% (94/679)
Warfarin alone	0.4% (3/714)	3.2% (22/679)
DOAC alone	6.0% (43/714)	66.7% (453/679)
Other medication regimen	0.1% (1/714)	0.1% (1/679)
None	8.5% (61/714)	4.0% (27/679)

HOW SUPPLIED

- The WATCHMAN FLX Device is pre-loaded in the Delivery System.
- The WATCHMAN FLX Device with Delivery System is supplied STERILE using an ethylene oxide (EO) process.
- WATCHMAN Access Systems are packaged separately.
- Do not use if package is opened or damaged.
- Do not use if labeling is incomplete or illegible.

Device Details

- Do not use if package is opened or 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 Device may be implanted.

Note: If choosing an ICE- and fluoroscopy-only procedure, pre-procedural planning with TEE or CT is recommended as utilized within the ICE-LAA study.

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 78** as a guide for size selection. Measured maximum LAA ostium width must be ≥ 14.0 mm and ≤ 31.5 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.

Note: In the OPTION clinical trial, the closure device implantation procedure followed catheter ablation, whether done sequentially or in the same procedure (concomitantly).

Note: Regardless of the energy source used, consider the potential for edema immediately following ablation and its impact to the WATCHMAN FLX landing zone. It is recommended to compare pre-procedural imaging to pre/post-ablation appendage morphology for device sizing.

PROCEDURE

Equipment Needed for Implantation Procedure

- Venous introducer (optional)
- Standard transseptal access system
- 0.035 inch (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)

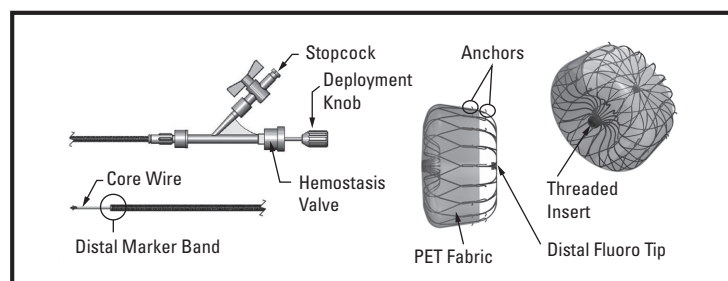


Figure 5. WATCHMAN FLX Delivery System (Delivery Catheter and Closure Device)

Implantation Procedure

Note: Aspirin should be started one day prior to scheduled procedure and continued daily, unless NOAC only is planned as the post procedure medication. If the physician intends to prescribe NOAC only for the patient post-procedure, pre-procedure aspirin usage is per physician discretion.

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 inch (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 inch (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. Insert Dilator into hemostasis valve of Access Sheath until the two snap together.

Warning: To reduce likelihood of negative left atrial pressures and air embolism, patients should not be hypovolemic, particularly if not under positive pressure ventilation such as general anesthesia.

Note: Do not tighten the hemostasis valve while the Dilator is inserted in the Access Sheath. The Dilator by itself will occlude the lumen of the Access Sheath, creating hemostasis. Tightening the valve onto the Dilator may damage the valve threads, which can lead to subsequent difficulty in closing the valve and an incomplete seal once the Dilator is removed.

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 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. Hold the hemostasis valve low, ensure it is fully open, remove Dilator and optionally remove 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 valve is fully open. 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.

Warning: If the patient is not under positive pressure ventilation such as general anesthesia, hold the hemostasis valve below heart level or submerged in fluid during device insertion to minimize low pressure and reduce the likelihood of air ingress. Withdraw devices slowly until the distal tip is near the valve, then complete the exchange during expiration.

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 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 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 78** 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 78**.

Table 78. WATCHMAN FLX 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

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

8. Prepare WATCHMAN FLX 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.

- C. Inspect prior to use to ensure there is no damage to hemostasis valve, catheter connections, or Closure Device (through Delivery System). Confirm 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 Closure Device with the deployment knob to assure it moves freely. While holding the Delivery System straight, position the distal tip of the Closure Device so that it is aligned with the Delivery System 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.

Note: To avoid introducing air, apply pressurized saline bag to sideport of Access Sheath, or submerge Access Sheath hub in saline. Saline may be dripped from Delivery System during introduction into Access Sheath by injecting through flush port.

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.

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. Hold the hemostasis valve low, and slowly remove pigtail catheter.
10. With the hemostasis valve of the Access Sheath low, loosen it, 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.

Warning: If the patient is not under positive pressure ventilation such as general anesthesia, hold the hemostasis valve below heart level or submerged in fluid during device insertion to minimize low pressure and reduce the likelihood of air ingress. Withdraw devices slowly until the distal tip is near the valve, then complete the exchange during expiration.

Note: Access Sheath hemostasis valve should spin freely (fully open).

Note: Tightening the Access Sheath hemostasis valve onto the WATCHMAN FLX Delivery System may damage the Delivery System or valve threads, which can lead to subsequent difficulty in closing the valve and an incomplete seal, once the WATCHMAN FLX Delivery System is removed.

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 fluoroscopic guidance, align most distal marker band on Delivery System 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 manifold must be attached to flush port of 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 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 Device must be in this initial deployment configuration when advancing the Access Sheath/Delivery System Assembly into the LAA without a pigtail.

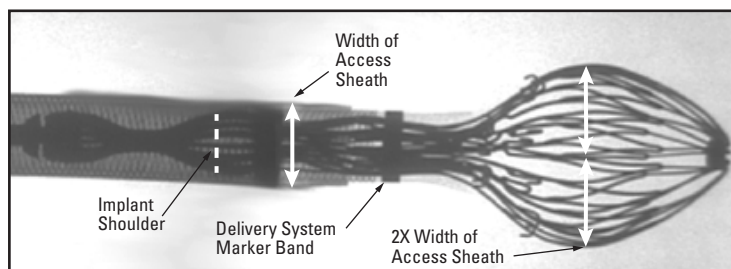


Figure 6. Initial deployment of the WATCHMAN FLX Device showing the proper configuration of the device and Implant shoulder reference for positioning the Closure Device within the LAA.

14. To fully deploy the Closure Device with the Implant shoulder aligned at the LAA ostium, the Advancement Method, the Unsheathe Method, or 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 shoulder 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 device from the Delivery Catheter, the Implant shoulder will align to the Delivery System distal marker band.

Note: Applying counterclockwise or clockwise torque to the Access Sheath may be beneficial during deployment to achieve proper alignment of the device relative to the ostium.

Note: Implant shoulder will become the plane of maximum Closure Device diameter (see Figure 6).

15. Closure Device release criteria: Position, Anchor, Size, and Seal (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.

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

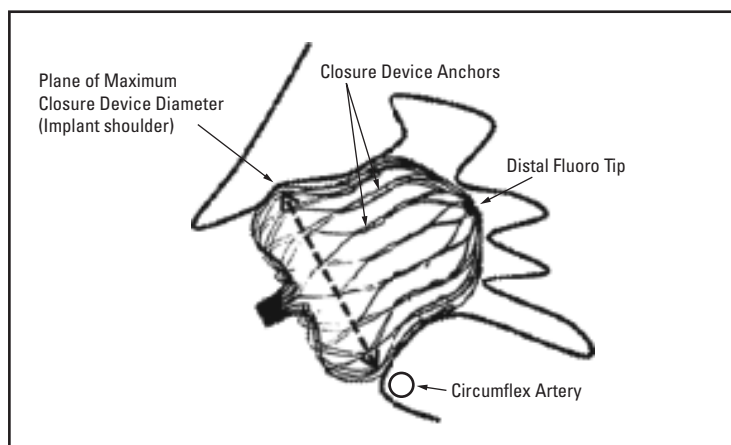


Figure 7. WATCHMAN FLX Device Position and Size

- B. **Anchor:** Gently pull back then release deployment knob to visualize movement of Closure Device and LAA together.
- C. **Size (compression):** Measure plane of maximum diameter of Closure Device (See Figure 7). Use Table 67 as a guide.
- D. **Seal:** Ensure all lobes of the LAA are distal to Closure Device and sealed (i.e., no leak > 5mm).

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 (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 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 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 Assembly until Closure Device is completely collapsed, recaptured, and distal fluoro tip is proximal to the marker band. Tighten Delivery System hemostasis valve.
- C. 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 Device.

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

- A. Confirm proper Closure Device release criteria: Position, Anchor, Size, and Seal (PASS criteria).
- B. Advance Access Sheath/Delivery System Assembly to face of Closure Device.
- C. Rotate deployment knob counterclockwise 3-5 full turns.
- D. Confirm core wire is disconnected.
19. Remove Access Sheath and Delivery System based on parameters for hemostasis.
20. 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:

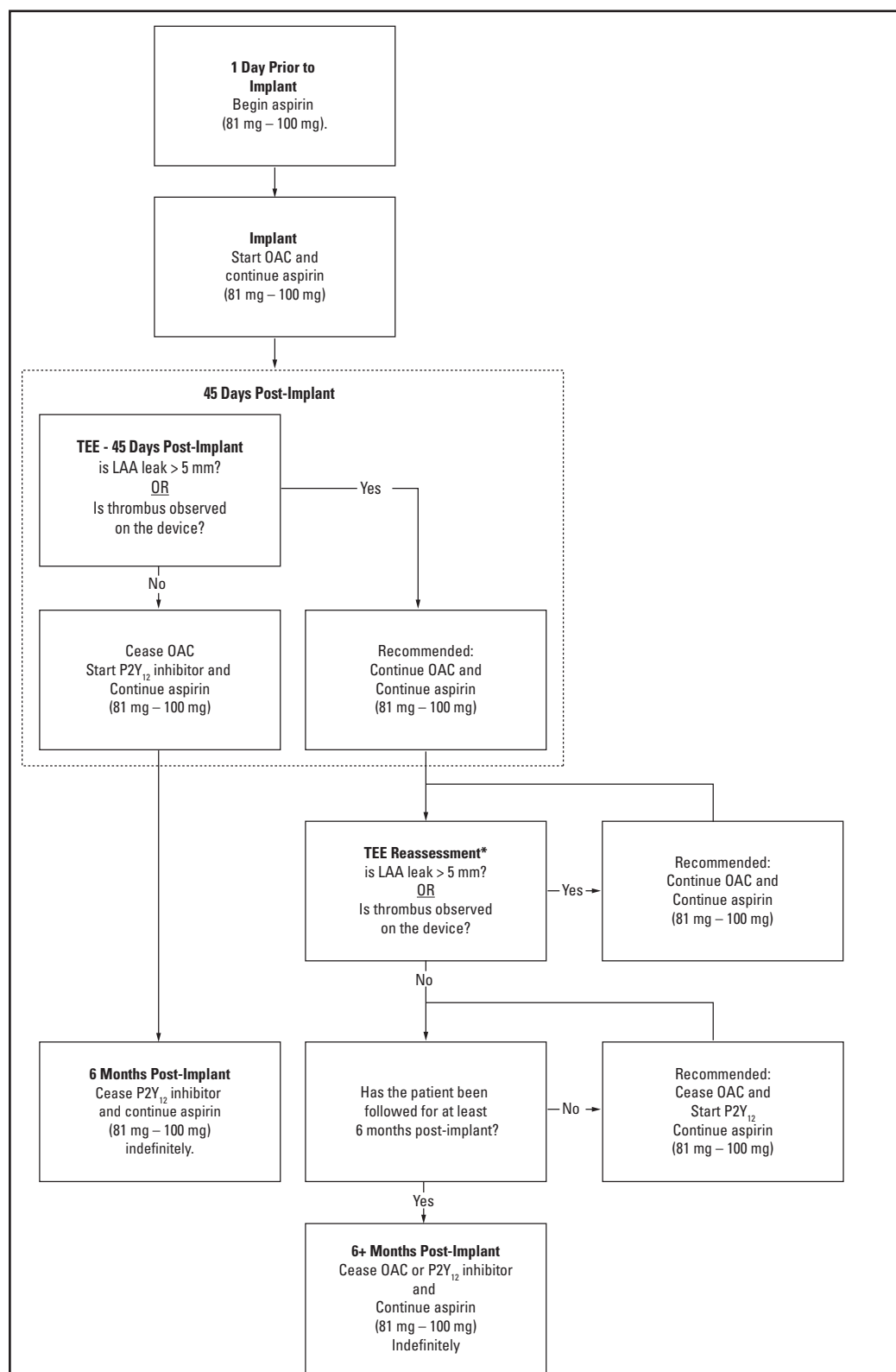
After use, device may contain biohazardous substances. The device and packaging should be treated and disposed of as biohazardous waste or have them treated and disposed of in accordance with any applicable hospital, administrative, and/or local government regulations. Use of a biohazardous container 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)

- OAC therapy should be started post-implant. If NOAC is chosen as OAC, the addition of aspirin is per discretion of the physician. At 45 days ($\pm$ 15 days) post-implant, perform WATCHMAN FLX Device assessment with TEE. Cessation of OAC therapy is at physician discretion provided that any leak demonstrated is $\leq$ 5 mm. If adequate seal is not demonstrated, subsequent OAC therapy cessation decisions are contingent on demonstrating leak is $\leq$ 5 mm. At the time the patient ceases OAC therapy, the patient should continue aspirin and begin a P2Y₁₂ 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 P2Y₁₂ inhibitor but should continue aspirin daily.
- At 45 days and at 12 months, perform imaging to assess the WATCHMAN FLX 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 anticoagulation therapy is recommended.
 - If thrombus is observed on the device, use of anticoagulation is recommended until resolution of thrombus is demonstrated by TEE.
- Prescribe appropriate endocarditis prophylaxis for 6 months following Closure Device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

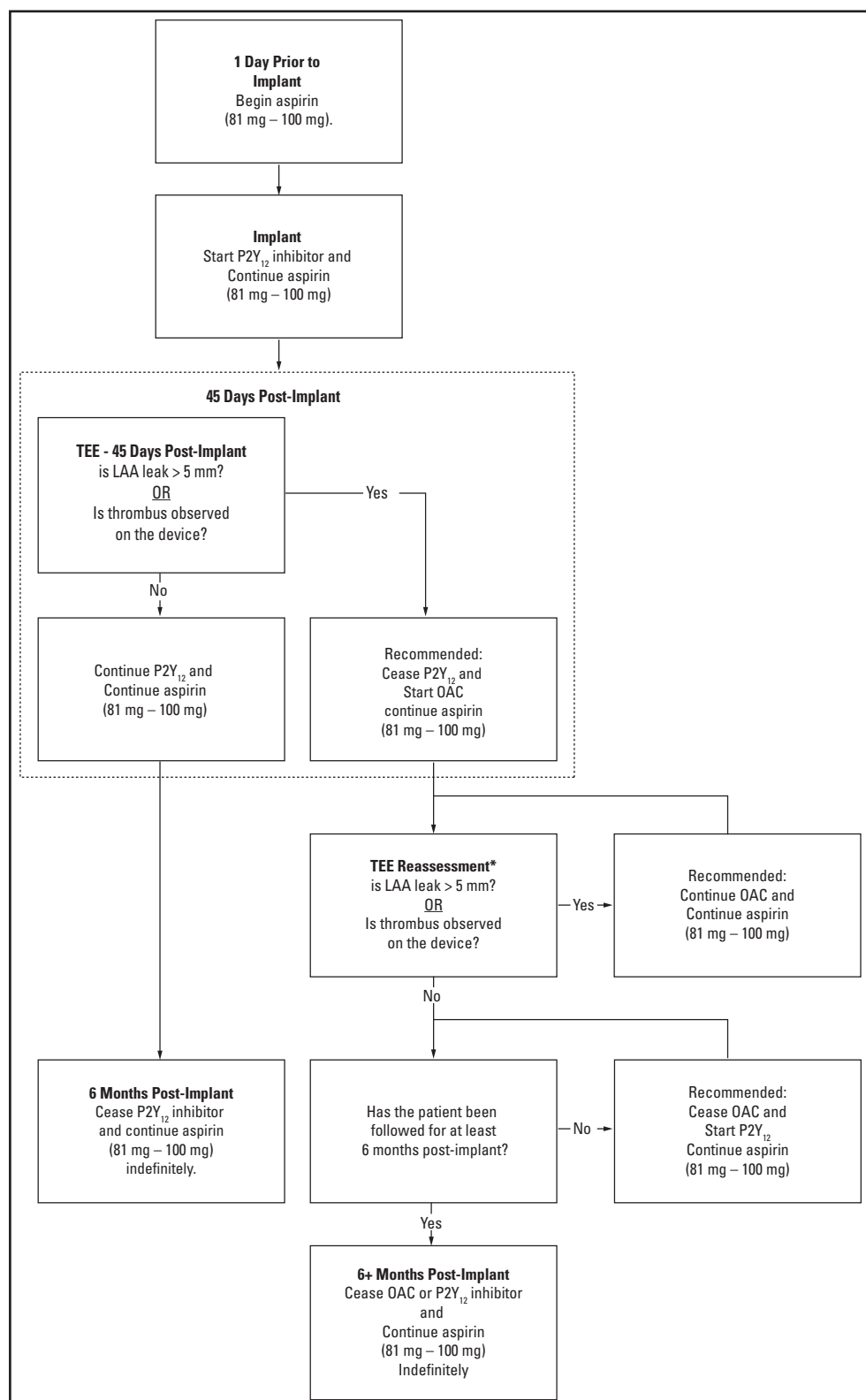


* The performance and timing of the LAA seal reassessment is left to physician discretion.

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

Option B) DAPT-only (see Figure 9)

1. Patients should remain on 81 mg – 100 mg of aspirin. P2Y₁₂ inhibitor therapy should be added post-implant. At 45 days (± 15 days) post-implant, perform WATCHMAN FLX Device assessment with TEE. P2Y₁₂ inhibitor therapy should continue for 6 months provided that any leak demonstrated is ≤ 5mm. If adequate seal is not demonstrated, discontinuation of P2Y₁₂ and starting OAC is recommended. Subsequent OAC therapy cessation decisions are contingent on demonstrating leak is ≤ 5mm. At the time the patient ceases OAC therapy, the patient should continue aspirin and re-start P2Y₁₂ 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 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 P2Y₁₂ 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.



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

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

Option C) Short-term OAC for Patients After Catheter Ablation for Non-Valvular Atrial Fibrillation Followed by WATCHMAN FLX Implantation (see Figure 10)

1. Patients should remain on 75 mg - 100 mg of aspirin. OAC therapy should be added post-implant. At 3 months ($\pm$ 15 days) post-implant, perform WATCHMAN FLX Device assessment with TEE or CT. Cessation of OAC therapy is at physician discretion provided that any leak demonstrated is $\leq$ 5 mm. If adequate seal is not demonstrated, subsequent OAC therapy cessation decisions are contingent on demonstrating leak is $\leq$ 5 mm. Patients should then remain on aspirin indefinitely.
2. At 3 and 12 months, perform imaging to assess the WATCHMAN FLX Device with TEE or CT.
 - 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 anticoagulation therapy is recommended.
 - If thrombus is observed on the device, use of anticoagulation is recommended until resolution of thrombus is demonstrated by TEE or CT.
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.

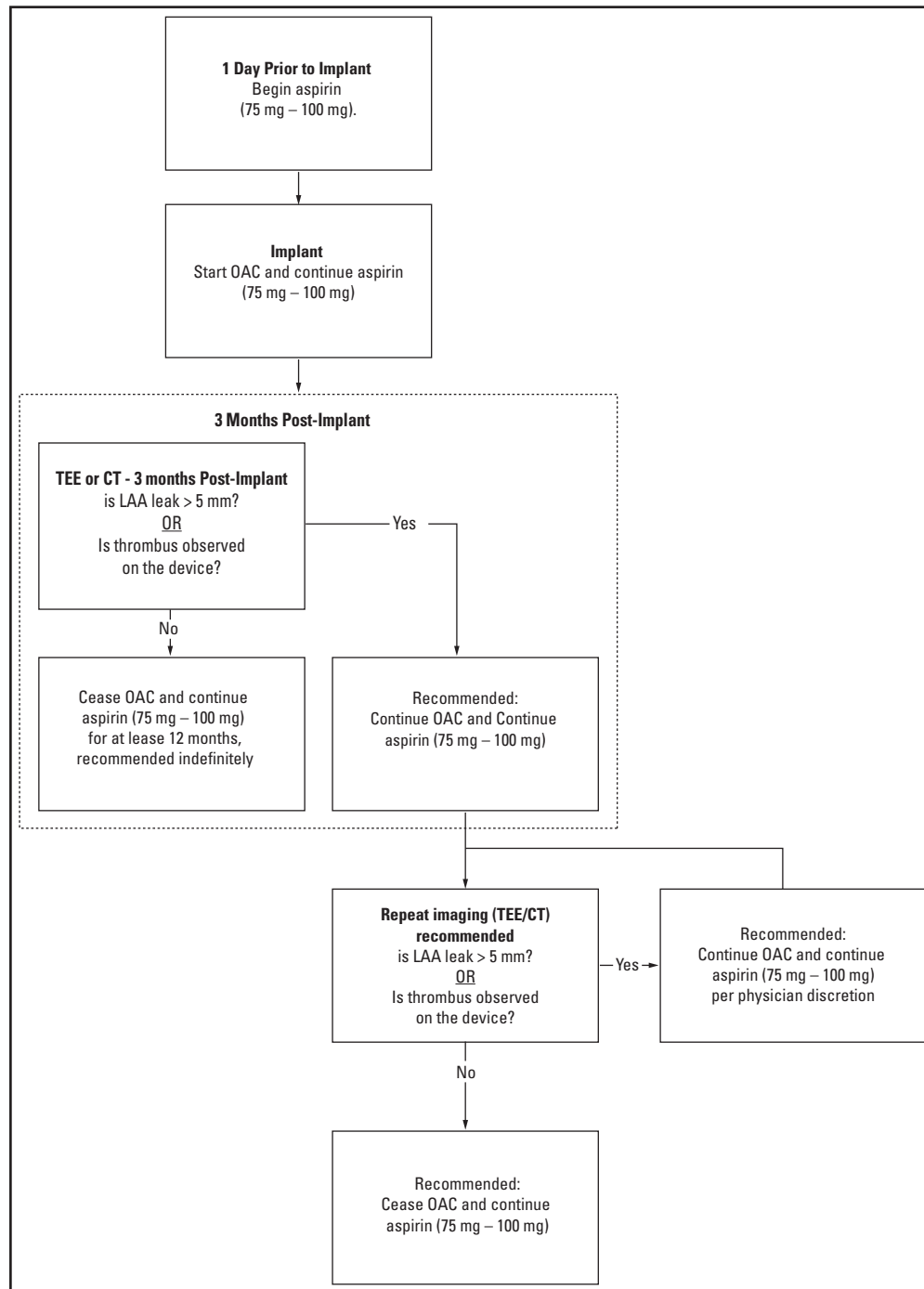


Figure 10. Option C) WATCHMAN FLX Device Pharmacologic Regimen (Short-term OAC for Patients Following Catheter Ablation for Non-Valvular Atrial Fibrillation Followed by WATCHMAN FLX implantation)

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).

The following are trademarks of Boston Scientific Corporation or its affiliates: PASS, WATCHMAN, WATCHMAN FLX.

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SYMBOL DEFINITIONS

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

Additional symbols are defined in **Table 79**.

Table 79. Symbol Definitions

	Contents
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EC REP

Boston Scientific Limited
Ballybrit Business Park
Galway IRELAND

AU REP

Boston Scientific (Australia) Pty Ltd
PO Box 332
BOTANY NSW 1455 Australia
Free Phone 1800 676 133
Free Fax 1800 836 666

AR REP

Para obtener información de
contacto de Boston Scientific
Argentina SA, por favor, acceda
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